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Testosterone Therapy of Male Eunuchoids

IV. Results from Methyl Testosterone Linguets

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IN A series of papers (1, 2, 3, 4) the principal author and several associates have contributed evidence establishing the clinical effectiveness of various testosterone compounds in the treatment of a highly specific endocrine deficiency, primary male hypogonadism or eunuchoidism. In successive reports the various modes of administering testosterone have been discussed and compared with regard to the convenience of dosage necessary for originating improvement and the maintenance of the benefits achieved. These publications included convincing photographic (before and after treatment) proof that the intramuscular injection of testosterone propionate, the implantation of methyl testosterone pellets, the peroral swallowing of methyl testosterone tablets and the sublingual absorption of testosterone compounds dissolved in propylene glycol—all were successful in correcting the severe genital retardation of primary hypogonadism.

In the last paper of this group (4) testosterone propionate, methyl testosterone and free testosterone, each dissolved in propylene glycol so that 0.2 cc. contained 5 mg., were administered sublingually in daily doses ranging from 10 to 25 mg. Six typical eunuchoids whose condition previously had been improved and who had been successfully maintained by parenteral, implantation, and/or oral administration of testosterone compounds, continued their improved states on sublingual testosterone. In only 1 of the 6 cases was the sublingual mode of therapy more economical in milligrams required than the peroral route. All of the patients preferred swallowing tablets to dropping a solution under the tongue.

Four hypogonadal patients who had not previously received any testosterone therapy derived striking benefits subjectively and objectively from the sublingual administration of testosterone compounds. Larger oral doses of methyl testosterone would have been required to initiate similar improvement. Sublingually, free testosterone was more effective than either methyl testosterone or testosterone propionate.

The present paper contains additional evidence of the effectiveness of therapy by the sublingual route. The new feature consists in

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the use of highly compressed tablets, each containing 5 mg. of methyl testosterone.[1] As a rule this tablet was placed under the tongue and kept there until dissolved. This might require 15 to 30 minutes. The patient was instructed not to swallow or expectorate during this absorptive period. Some patients found it more convenient to place the tablet between the gum and the cheek, near the second molar. Several of the patients had had previous experience with the sublingual method when testosterone compounds had been dissolved in propylene glycol. All were unanimous in considering the compressed tablet a more convenient and pleasant tasting vehicle than the propylene glycol solution. An additional advantage was the higher potency of these linguets, since almost uniformly, a decidedly smaller daily dose sufficed to maintain their improved status. The only reference to linguet treatment with methyl testosterone in male hypogonadism which we have discovered is the single case report of Spence (5). The patient was a man, aged 23 years, who had been castrated in childhood. After initial heavy dosage of testosterone propionate parenterally, he had been maintained satisfactorily on a peroral dose of 15 mg. daily of methyl testosterone. Spence found that two 5 mg. methyl testosterone linguets daily maintained equal benefits.

Herewith follow the protocols of 12 cases. Six of the 12 cases included in this series have been reported in previous papers (1, 2, 4) in more elaborate detail. The patients in these 6 cases were characteristic examples of severe eunuchoidism which originated prior to the age of normal adolescence; they had been exceedingly immature at the ages of 24, 24, 31, 24, 29.5 and 21 years, respectively. Subsequently they had been treated with testosterone, administered parenterally or by implantation, by tablets perorally, or by solution sublingually. They had all been vastly improved and successfully maintained by means of one or more of these procedures. Since they had been observed for a sufficiently long period of time to permit critical comparative appraisal of parenteral, implantation, oral and sublingual administration of testosterone compounds, we considered them excellent controls for a trial of methyl testosterone linguets.

The remaining 6 patients in this series represented several types of male hypogonadism. None of these cases, except *Case 12*, had been reported (6), and some of them had not received any form of testosterone therapy before. All of them displayed striking improvement from therapy with methyl testosterone linguets. No other treatment was given. We believe, therefore, that the benefits achieved may be properly ascribed to the administration of the methyl testosterone linguets.

CASE REPORTS

Case 1; R.C. (U 57397). *Case 7* in (1); *Case 1* in (2) with photographs; *Case 1* in (4). The patient was 24 years old when first seen in April, 1940. His appearance was characteristic of that of pre-adolescent eunuchoidism. He had typical disproportionately long extremities, shaved infrequently and had a high-pitched voice. The pubic hair was scant and axillary growth was moderate. The penis was small (length 5 cm.); the testes were the size of small olive pits. The left testis was undescended. The prostate was barely palpable. The bone age was 16 to 17 years at 24 years of age.

Between April, 1940, and May, 1941, he had improved greatly with implantations of methyl testosterone, the dose varying from 143 to 800 mg. The stimulating effects of the individual implants lasted from 4.5 weeks to 5 months.

Between May, 1941, and April, 1942, the patient received either methyl testosterone, testosterone propionate, or free testosterone, dissolved in propylene glycol and administered sublingually in doses of 5 mg. four times daily. A survey of the 11 months of sublingual therapy showed that the patient had lost ground somewhat, more especially in the subjective sphere,[2] although the size of the external genitalia had not diminished.

In April, 1942, linguets were substituted, using, methyl testosterone in compressed 5-mg. tablets,

[1] These methyl testosterone linguets were furnished for this study by Ciba Pharmaceutical Products, Inc., Summit, N. J.

[2] As stated on page 634 in the paper by Escamilla and Lisser on "Testosterone Therapy of Eunuchoids," *J. Clinical Endocrinology* 1: 633. 1941: "The subjective changes consist of an increased feeling of well-being, better appetite, development of self-confidence, greater initiative, more energy and endurance, cheerfulness instead of moodiness, and optimism instead of depression. The patient is further encouraged by his ability to obtain a position or promotion in labor or business endeavors. Convincing also is the onset or markedly increased frequency of erections, the appearance of nocturnal emissions, and the desire to masturbate or seek sexual intercourse. Less conspicuous, but occasionally noted, is the disappearance of headaches and indigestion. Rarely, the incidence of convulsive seizures may be diminished."

4 times daily. During the succeeding 8 months, two attempts were made to reduce this dose to 10 or 15 mg. daily. The former dose of 20 mg. daily had to be resumed as on both trials of reduced dosage the hair growth seemed to stop, erections and libido diminished and weight was lost.

In this typical eunuchoid, four 5-mg. linguets of methyl testosterone daily maintained a satisfactory status, both subjectively and objectively. This dose is the same as that used when testosterone was dissolved in propylene glycol and administered sublingually, but is 10 mg. less than when methyl testosterone tablets were used perorally.

It is noteworthy, also, that although this patient had received intensive testosterone treatment for two years prior to linguet therapy, the penile dimensions increased considerably during this latter regime (fig. 1, A, B and C). These observations regarding linguet therapy covered a period of 10 months.

Case 2; L.K. (U 20634). Case 3 in (1); *Case 3* in (2) with photographs; *Case 2* in (4). The patient was 24 years old when first seen in September, 1937. He had the disproportionately long arms and legs of a typical eunuchoid. He had never shaved and his voice was high-pitched. The pubic hair was sparse and only a very few axillary hairs were present. The penis was small (length 4.75 cm.) and the scrotal content consisted of some questionable tissue in the left side. The bone age was 15 years at 24 years of age.

He was vastly improved by 16 months of parenteral administration of testosterone propionate, a total of 3500 mg. In the following year (November, 1939, to November, 1940) the patient received 5 implants of methyl testosterone, the dosage ranging from 101.3 mg. to 164 mg. per implant. The previously attained improvement was adequately maintained, both subjectively and objectively. This was likewise accomplished between November, 1940, and May, 1941, by the peroral consumption of 30 mg. daily of methyl testosterone. Subsequently, between May, 1941, and April, 1942, his improved status was equally well maintained by one-half this amount, 15 mg. daily, administered as free testosterone dissolved in propylene glycol and absorbed sublingually.

In April, 1942, linguets were substituted, using methyl testosterone in compressed 5-mg. tablets, 15 mg. daily. In September, 1942, this dose was reduced to 10 mg. daily and this amount proved adequate to insure satisfactory intercourse once a week. He mentioned slight tenderness of the nipples. The size of the genitalia remained the same. He had noticed definite darkening of the beard. There was no change in body weight.

In this typical eunuchoid, two 5-mg. linguets of methyl testosterone daily maintained a satisfactory status, both subjectively and objectively. These observations regarding linguet therapy covered a period of 6 months.

Case 3; J.J. (U 36521). Case 4 in (1) with photographs; *Case 4* in (2); *Case 4* in (4). The patient was 31 years old when he was first seen in May, 1938. He had typical pre-adolescent eunuchoidism with disproportionately long extremities; the height was 71 in. and weight 123 lb. The voice was high-pitched; he had

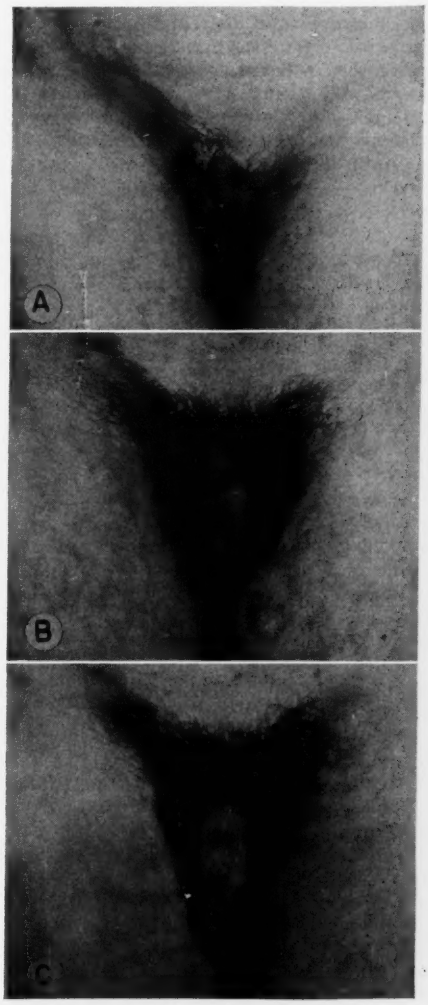

FIG. 1. PRE-ADOLESCENT EUNUCHOIDISM. *Case 1, R.C.* Age 24 yr. *A.* April, 1940. *B.* January, 1942. Testosterone implants and sublingual testosterone therapy from April, 1940 to January, 1942. *C.* October, 1942. April to October, 1942, 4 linguets, 20 mg., of methyl testosterone daily.

a few axillary hairs and a moderate amount of pubic hair. He clipped the fuzz from his face every 2 to 3 weeks. The penis was small (length 4.5 cm.). Testes and scrotum were very small; the prostate was not palpable. The bone age was 18 years at 31 years of age.

He was vastly improved by parenteral administration of testosterone propionate, receiving 3800 mg. between January, 1939, and February, 1940. These

benefits were maintained in the succeeding 9 months by 4 implants of methyl testosterone varying in size from 102.7 to 148.1 mg. Between November, 1940, and April, 1941, the improved status was continued by the peroral use of 30 mg. daily of methyl testosterone. Between April, 1941, and April, 1942, methyl testosterone, testosterone propionate and free testosterone, each dissolved in propylene glycol, were administered sublingually. In this patient, doses of 15 mg. daily, sublingually, were far less effective than 30 mg. perorally.

In April, 1942, linguets were substituted, using methyl testosterone in compressed 5-mg. tablets, 15 mg. daily. Subsequently, this dose was reduced to 10 mg. daily, and later to 5 mg. daily, and finally to 5 mg. every other day. This small amount, in the form of a linguet, maintained a satisfactory status, both subjectively and objectively, quite remarkably, considering the infantile condition of this typical eunuchoid at 31 years of age. These observations regarding linguet therapy covered a period of 7 months.

Case 4; F.V. (U 62077). Case 6 in (2) with photographs; *Case 5* in (4). The patient was 24 years old when first seen in July, 1940. He had disproportionately long extremities and looked younger than his stated age. His voice was high-pitched, he had scant axillary and pubic hair and no beard or other body hair. The penis was small (length 4 cm.); the testes were small and soft; the prostate was about two-thirds normal size. The bone age was 16 years at 24 years of age.

In August, 1940, he received an implant of 117 mg. of methyl testosterone; in September, 1940, a second implant of 122.9 mg.; and in November, 1940, a third implant of 600 mg. The stimulating effects of this last implant had subsided entirely 11 weeks later. Between February and June, 1941, the status of the patient was successfully maintained by the peroral use of 30 mg. daily of methyl testosterone. Between June, 1941, and April, 1942, fairly satisfactory results were obtained from the sublingual administration daily of 15 mg. of free testosterone dissolved in propylene glycol.

In April, 1942, linguets were substituted using methyl testosterone in compressed 5-mg. tablets, 15 mg. daily. Subsequently, this dose was reduced to 10 mg. and later to 5 mg. daily. In this typical eunuchoid one 5-mg. linguet of methyl testosterone per day maintained a satisfactory status, both subjectively and objectively. These observations regarding linguet therapy covered a period of 6 months.

Case 5; S.S. (U 72982). Case 8 in (4) with photographs. The patient was first seen on June 9, 1941, at the age of 29.5 years. He looked like an elderly boy. He had no beard. The pubic escutcheon was relatively sparse and of feminine type and the axillary hair was scant. The genitalia were infantile; the penis was tiny, measuring 2.5 cm. in length and 4.5 cm. in circumference; the scrotum was empty; the prostate was not palpable.

Between June, 1941, and April, 1942, he received testosterone compounds sublingually (dissolved in propylene glycol) in doses of only 12.5 mg. daily. Improvement, both subjectively and objectively, was remarkable, considering the relatively small dosage and the fact that he had not received any other form of testosterone therapy prior to this. Previous experience in comparable cases of severe primary hypogonadism indicated that at least four times this amount daily would have been required to achieve equivalent improvement if the treatment had consisted of oral ingestion of methyl testosterone tablets.

In April, 1942, linguets were substituted using methyl testosterone in compressed 5-mg. tablets, 10 mg. daily. With this dosage the patient's voice became deeper and huskier and the hair growth in the axillae and on the arms and legs increased noticeably. The patient appeared more mature and behaved accordingly. Subsequently, the daily dose was reduced to one 5-mg. linguet daily, without diminishing the patient's weight, strength, or energy. However, he noted a decreased amount of ejaculate from masturbation.

In this typical 30-year-old eunuchoid, one 5-mg. linguet of methyl testosterone per day maintained a satisfactory status, both subjectively and objectively. These observations regarding linguet therapy covered a period of 10 months.

Case 6; B.C. (U 4545). Case 6 in (1) with photographs; *Case 5* in (2); *Case 3* in (4). This patient was first seen in March, 1933, when he was 17 years old. He was a characteristic example of pre-adolescent eunuchoidism with small genitalia, complete absence of secondary sex manifestations and disproportionately long extremities. During the next 3.5 years, various endocrine preparations were tried with negligible effect.

Between November, 1936, and November, 1939, he was vastly improved by parenteral administration of testosterone propionate, totalling, 10,250 mg. These benefits were maintained and enhanced in the succeeding 8 months by 3 implants varying in dosage from 109.6 to 138.3 mg. Between November, 1940, and April, 1941, the peroral administration of methyl testosterone in 10-mg. tablets, at first using 30 mg. daily, subsequently, 20 mg. daily and later, 10 mg. daily, sufficed to maintain him in a satisfactory condition. Between April, 1941, and April, 1942, methyl testosterone, testosterone propionate and free testosterone, each dissolved in propylene glycol, were administered sublingually. In this patient a sublingual dose of 10 mg. daily had an effect neither greater nor less than an oral dose of 10 mg.

For the succeeding 6 months this patient received no treatment whatsoever. For the first 3 months of this period, the sexual and general status remained unaltered. Gradually, during the next 3 months, the frequency of erections diminished and the penis decreased in size from 12.25 cm. to 10.5 cm. in length. He was instructed to try the effect of one 10-mg.

tablet daily of commercial methyl testosterone, placed under the tongue. Six weeks later he reported improvement and volunteered the belief that this dose absorbed sublingually was more potent than when swallowed. The penis had regained the former dimensions.

At this time he was instructed to substitute one 5-mg. linguet of methyl testosterone for the 10-mg. tablet. This dose proved equally effective.

Case 7; *D.N.* (*U 83782*). This patient, a 36-year-old man, was first seen on May 11, 1942. He complained of lack of sexual development which had been untreated until March, 1941. Between March, 1941, and August, 1941, he had received 1000 mg. of testosterone propionate. This had been given in twice weekly injections of 25 mg. each, alternating with injections of an anterior pituitary preparation. On the days when he received no injection he took 20 mg. of methyl testosterone by mouth. This treatment produced deepening of the voice and growth of pubic and axillary hair.

The patient was 72.5 in. tall and weighed 188.5 lb. The span was 74 in. and the lower measurement was 38 in. from the pubis to the soles of the feet (fig. 2, A). His face was finely wrinkled, with a fawn colored complexion. Beard was practically non-existent. There was a well marked gynecomastia. The axillary hair was sparse, but the pubic escutcheon was heavy and female in distribution. The scrotum was small and retracted. Both testes were in the inguinal canals. Each testis was about the size of a small olive. The penis measured 3.5 cm. long by 7 cm. in circumference (fig. 2, B). The B.M.R. was −7 per cent. The Kahn and Kolmer reactions were negative.

On May 14, 1942, administration of methyl testosterone in 5-mg. linguets, was started in a dosage of 20 mg. daily. By June 25, 1942, he was having 4 or 5 erections daily, which was very annoying. He had had one nocturnal emission and successful intercourse twice. The dosage was therefore reduced to 10 mg. daily. With this amount he had erections when stimulated and held intercourse about every two weeks. On Nov. 19, 1942, the penis measured 5 cm. long by 8 cm. in circumference (fig. 2, C). At this time the dosage was increased to 15 mg. daily. When seen one month later, the patient felt much better on this increased dosage, and the improved sexual status was successfully maintained. These observations regarding linguet therapy covered a period of 9 months.

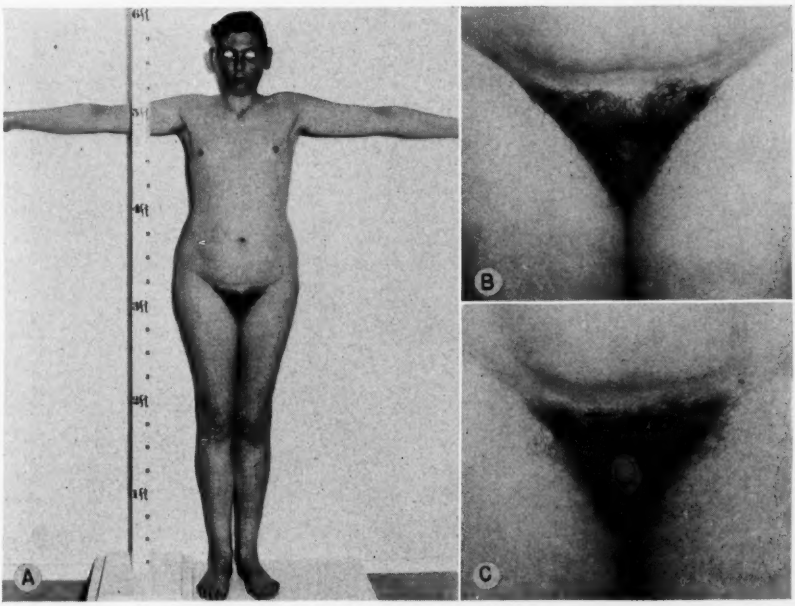

FIG. 2. PRE-ADOLESCENT EUCHNUCHOIDISM. *Case 7*, *D.N.* Age, 36 yr. *A*, *B*. May, 1942. *C*. November, 1942. Methyl testosterone linguets, 10–15 mg. daily from May, 1942, to November, 1942.

Case 8; T.H. (*U 88717*). This patient was first seen on Oct. 16, 1942, at the age of 19 years, 7 months. He complained of sexual impotence. His development and growth were normal until the age of 16.5 years. At the age of 13 years, one testicle became swollen for no apparent reason and was surgically drained. At the age of 16.5 years, a similar episode occurred involving the other testicle. Following the second attack, he noticed marked loss of strength, cessation of erections and emissions, and failure to develop further male charac-

teristics. About one year before admission to the clinic, he was given injections of testosterone propionate, 25 mg. twice a week, over a period of 3 months. During that time the patient gained weight and felt much stronger. His beard began to grow and he had daily erections, but no emissions. He had been untreated since January, 1942, and noted decreased energy, regression of his beard, cessation of erections, and a loss of 10 lb. in weight.

The patient was an asthenic boy with a moderately high-pitched voice. There was a rather marked, coarse, involuntary tremor of the hands. He was 68.25 in. tall and weighed 127.4 lb. His span was 68 in. and lower measurement, from pubis to soles, was 33.25 in. He had no beard, and the pubic escutcheon was feminine in type. The penis measured 8.5 cm. long and 8 cm. in circumference. Neither testis could be seen or felt; the prostate felt small and flat. Evidently the bilateral orchitis resulted in complete atrophy of both testes. His condition was classified as "post-adolescent post-infectious hypogonadism." However, the pubic hair had not dropped out and the penis had not shrunk to any marked extent. The B.M.R. was +13 per cent. The glucose tolerance was normal.

On Nov. 14, 1942, treatment was started with methyl testosterone using 5-mg. linguets, in a dosage of 15 mg. daily.

After 6 weeks of therapy the patient had gained 13.5 lb. in weight and felt much more energetic. Erections were occurring every other day, but there had been no emissions nor inclination to masturbate. At this time the dose was reduced to two 5-mg. linguets daily.

One month later, Jan. 21, 1943, the patient reported fewer erections. However, he had continued to gain weight, an additional 7.5 lb., making a total of 21 lb. in a period of almost 10 weeks!

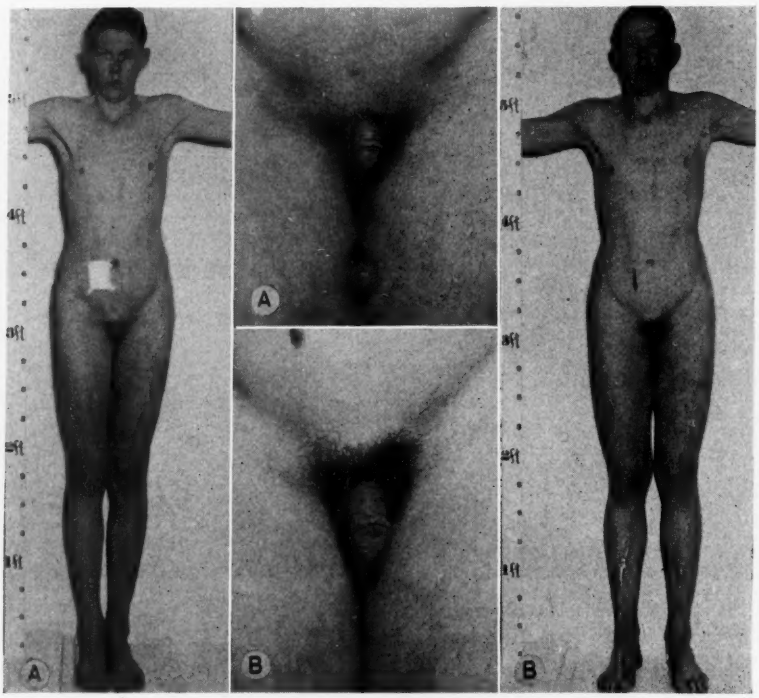

FIG. 3. PRE-ADOLESCENT EUNUCHOIDISM. *Case 9*, age 19 yr. 4 mo. *A*. November, 1942. *B*. February, 1943. Methyl testosterone linguets, 15 mg. daily. Gauze dressing covers recent appendectomy incision. Right side of pubic escutcheon shaved from November, 1942, to February, 1943.

Case 9; *L.V.* (*U 89573*). A boy 19 years and 4 months old, was first seen on Nov. 11, 1942. He complained of bilateral cryptorchidism and lack of sexual development. Four weeks before admission he underwent an operation for acute appendictis. Otherwise the past history was negative.

The patient was 70.4 in. tall and weighed 133.75 lb. His span was 74.6 in. and the lower measurement 38 in. from the pubis to the soles of the feet. There was no beard. Axillary and pubic hair was sparse and the pubic hair on the right side had recently been shaved for the appendectomy. The penis measured 4.5 cm. long by 6.5 cm. in circumference. The scrotum

was small and retracted. No testes were palpable in the scrotum or inguinal canals. The prostate was poorly developed. The B.M.R. was +5 per cent; the bone age, 15 years, a retardation of about 4 years.

On Nov. 12, 1942, administration of methyl testosterone in 5-mg. linguets was initiated using a dosage of 15 mg. daily. On Dec. 10, 1942, one month after starting therapy, the patient weighed 145.25 lb.; this was a gain of 11.5 lb. One month later, on Jan. 7, 1943, he had gained an additional 8.5 lb., weighing 153.75 lb. Erections occurred two or three times daily and the penis measured 9 cm. long by 10 cm. in circumference. In general he felt much stronger and more energetic. The testes could not be felt.

When last seen, Feb. 20, 1943, he weighed 159.25 lb., a total gain of 25.5 lb. in 3.5 months! During this same period he grew 7/8 in. (fig. 3, A). The remarkable growth of the penis and pubic hair is apparent in figure 3, B.

Case 10; J.F. (U 80642). This patient was first seen on Jan. 29, 1942, at the age of 43 years, 5 months. He complained of lack of skeletal growth and failure to develop secondary sexual characteristics. He was born in Russia and had always had good health. He had never had any facial or pubic hair and only very little axillary hair. Occasionally he experienced erections when he thought about women or took hot

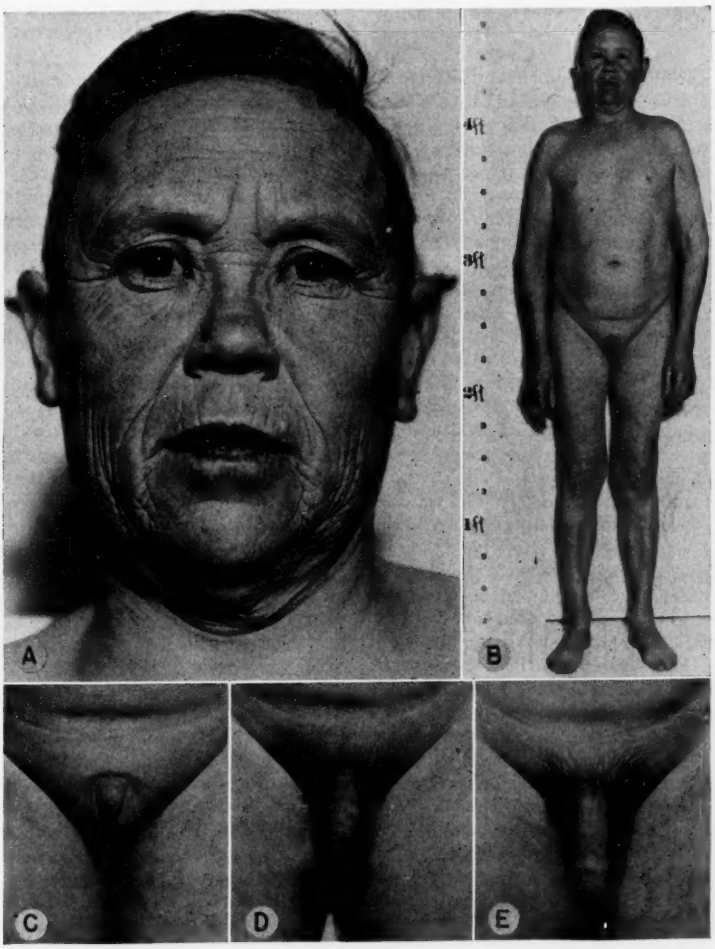

FIG. 4. PRIMARY HYPOGONADISM WITH SHORT STATURE. *Case 10, J.F.* Age, 43 yr. *A, B, C.* January, 1942. Methyl testosterone, 10-mg. tablets perorally, 100 mg. daily. *D.* June, 1942. *E.* October, 1942. Methyl testosterone, 5 mg. linguets, originally 25 mg. daily, gradually reduced to 5 mg. daily from June, 1942, to October, 1942.

showers, but he had never had intercourse or masturbated and had had no nocturnal emissions.

The other members of his family were of average size and developed normally except for a brother two years older who was suffering from the same conditions as the patient.

The patient was a short man (height 58.25 in.) looking considerably older than his stated age. His face was deeply wrinkled and beardless (fig. 4, A and B). The skin was fine textured and dry. The hair was fine and normally oily. The weight was 102.25 lb.; span, 62.25 in.; the lower measurement from pubis to soles, 30.75 in. There was no pubic hair and the axillary hair was very sparse. The penis measured 3.5 cm. long by 4.75 cm. in circumference (fig. 4, C). The testes were of lima-bean size and retracted easily into the inguinal canals. The prostate could not be palpated. The B.M.R. was −12 per cent. The bone age was 16 years at 43 years of age. Urine creatine, none; urine creatinine, 790 mg.

Oral methyl testosterone therapy was started Feb. 12, 1942, in a dosage of 100 mg. daily. After 3 days of treatment erections occurred 6 or 7 times daily, but no emissions. On June 24, 1942, after 4.5 months on this dosage, the patient weighed 109.25 lb., a gain of 7 lb. His voice was much deeper, and considerable pubic hair had appeared. The scrotum was more relaxed and corrugated. The penile measurements had increased from 3.5 cm. and 4.75 cm. to 7 cm. in length and 8 cm. in circumference (fig. 4, D). The prostate could now be palpated as a definite organ about 2 cm. in diameter.

At that time, June 24, 1942, treatment was changed to methyl testosterone in 5-mg. linguets using 25 mg. daily. By July 9, 1942, there had been no subjective change on this markedly reduced dosage, and the penis measured 8 cm. long by 8.5 cm. in circumference. Erections continued 4 or 5 times daily. Therefore, the dosage was reduced to 3 linguets, 15 mg. daily. After 2 months on this dosage, the erections had decreased to 2 or 3 daily, but the pubic hair growth had increased. On Sept. 9, 1942, the dose was again reduced, to 2 linguets, 10 mg. daily. The penis and pubic hair continued to grow as is evident in figure 4, E, taken in October, 1942. Since there was no change for the worse after 5 weeks on this dosage, it was further reduced to 1 linguet, 5 mg. daily. On this small amount erections decreased to 2 or 3 times a week, but there was no loss of general strength or energy. On Jan. 28, 1943, the weight had decreased to 106 lb. The penis measured 7.5 cm. long by 9 cm. in circumference. During the year of testosterone therapy the patient grew 3/8 in. despite his age of 43 years.

Case 11; A.R. (*U 85578*). A 73-year-old man was first seen on July 16, 1942. He complained of hot flushes, melancholia, nervousness, emotional instability with frequent weeping spells, ankle edema and marked decrease in mental activity and ability. One year previously bilateral orchidectomy had been performed because of an injury to the scrotum and testes. Within 2 days after the operation, all of the above symptoms began to appear. He noticed, also, that the pubic hair failed to grow as vigorously as previously, and he became more sensitive to cold. Libido decreased, although partial erections still occurred once or twice a week. His weight increased from 176 to 183 lb. and the fat was distributed about the abdomen more than ever before. The hot flushes were usually precipitated by exertion, or any type of emotion. They lasted about 2 minutes and occurred from 20 to 40 times daily.

He had always been energetic and alert mentally, as an actor, author and playwright, but since castration had lost all amibiton, zest and ability to concentrate.

The patient looked several years younger than his stated age of 73 years. He was quite emotional and occasionally burst into tears during the interview and examination. There was a loud, rasping systolic murmur over the apex of the heart, transmitted to the axilla and to the base of the heart. The blood pressure was 175/85 mm. Hg. Both testes were surgically absent. There was a left, direct, inguinal hernia. Marked edema of the feet and ankles extended 2/3 of the distance upward to the knees. Blood and spinal fluid Wassermann reactions were positive.

On July 16, 1942, he was given digitalis, 0.2 gram daily, and phenobarbital, 0.03 gram twice daily. On Aug. 6, 1942, he was having some nausea and visual disturbance, but the therapy was continued. In addition, testosterone propionate hypodermically was started in a dosage of 25 mg. once a week. He received 5 such injections and felt some better. However, his 'climacteric' symptoms would recur before the week had elapsed between injections.

On Sept. 3, 1942, he was given one 5-mg. linguet of methyl testosterone daily, and the injections were discontinued. The digitalis and other cardiac therapy was maintained, plus mercupurin, in spite of nausea. By Oct. 1, 1942, the melancholia had practically vanished and he had no more hot flushes.

Because of several favorable reports (7, 8, 9, 10) in recent medical journals regarding male hormone therapy in older men suffering from cardiovascular ailments, it was deemed opportune to test the cardiovascular effectiveness of testosterone therapy in this patient by confining treatment entirely to administration of methyl testosterone linguets. Accordingly, on Oct. 1, 1942, treatment with digitalis, mercupurin, and phenobarbital, were suspended.

At the end of 3 weeks of therapy with methyl testosterone linguets only the ankle edema was almost entirely gone, the pulse was normal and regular, he was no longer having hot flushes, his mental activity was almost normal, and he was not emotional or melancholic. On Dec. 17, 1942, he was still noting some ankle edema when on his feet a long time. The dyspnea had diminished markedly. Erections occurred practically every morning and he had erotic dreams about once a week.

On Jan. 7, 1943, the patient reported some waning

of effects of therapy with some return of the hot flushes. Consequently, the dose was increased to two 5-mg. linguets, 10 mg., daily. Three weeks later the patient reported that with the increased dosage the flushes had ceased almost immediately, the melancholia vanished, and that there was a decrease in palpitation, dyspnea and nocturia. However, the ankle edema had increased somewhat.

Case 12; K.K. (U 70442); (6) with photographs. This patient was first seen in March, 1941, when 29 years old. His condition was recognized as acromegaly of about 4 years' duration. Gradual, and finally, total loss of libido and potentia had developed between October, 1940, and March, 1941; some diminution in the size of the genitalia had been noted by the patient.

During April and June, 1941, two courses of pituitary irradiation were administered consisting of 1800 and 2700 roentgens, respectively. The benefits derived were manifested by disappearance of somnolence, lethargy, polyuria, polydipsia, polyphagia and headaches, plus improvement of visual acuity and restoration of normal visual fields. However, the patient's strength and energy were still below par and libido and potentia remained absent.

In view of the remarkable results achieved in the rehabilitation of eunuchoids by testosterone therapy, and because experimental work (11, 12, 13) suggested that such treatment might inhibit the hyperactivity of an anterior pituitary adenoma, testosterone propionate was given parenterally in 25-mg. doses three times a week for 3 months, the total dose being 850 mg. The improvement was dramatic; libido and potentia were restored completely, and strength and vigor had returned so that the patient was able to resume his occupation as a roofing estimator. Subsequently, his improved status was maintained by methyl testosterone orally in doses of 40 mg. daily, and later 20 mg. daily.

On June 25, 1942, therapy was started using two 5-mg. linguets of methyl testosterone daily. Subsequently, this dose was increased to 15 mg. daily and proved adequate for the following 4 months. On Jan. 7, 1943, the patient volunteered the observation that he felt better when taking 15 mg. daily of methyl testosterone in linguets than with 30 mg. daily perorally.

SUMMARY OF CASES AND DISCUSSION

The purpose of this investigation was to determine whether highly compressed tablets of methyl testosterone, designed for slow sublingual absorption, would: *a*), maintain the improvement previously produced and maintained in cases of severe eunuchoidism by administration of testosterone propionate intramuscularly, by implantation of methyl testosterone pellets subcutaneously, by administration of methyl testosterone tablets perorally and/or by the sublingual absorption of testosterone dissolved in propylene glycol; *b*), initiate an improved sexual status subjectively and objectively in hypogonad individuals who had not previously received any form of testosterone therapy; *c*), reveal the advantages or disadvantages, economically and otherwise of the use of linguets as compared to parenteral, implantation, peroral, or the absorption sublingually of a testosterone solution. We believe that our experience in the 12 cases reported provides an adequate answer to these three considerations.

The effectiveness of methyl testosterone linguets as a maintenance regime was tested in 7 patients, all of whom had been typical examples of severe pre-adolescent eunuchoidism and who had been exceedingly immature at the ages of 24, 24, 31, 24, 29.5, 21, and 35 years, respectively. At the time methyl testosterone therapy in the form of linguets was initiated they had been vastly improved by other forms of testosterone therapy. They had reached the ages of 26, 29, 35, 26, 30, 26, and 36 years, respectively.

In *case 1*, the patient progressed satisfactorily using 20 mg. of testosterone linguets daily, an amount equivalent to that which was effective when administered sublingually in propylene glycol, but which was 10 mg. less than the amount required when methyl testosterone tablets were swallowed. However, further genital development occurred despite 26 years of age, previous testosterone implants and sublingual therapy (fig. 1, *B* and *C*).

In *case 2*, the patient maintained a satisfactory status, both subjectively and objectively, on two 5-mg. linguets of methyl testosterone, as compared to 15 mg. daily sublingually when the propylene glycol solution was employed, and 30 mg. daily when methyl testosterone tablets were swallowed.

In *case 3*, the patient, originally an example of a very sever primary gonadal deficiency, was maintained satisfactorily on one 5-mg. linguet of methyl testosterone daily. This small dose was more effective than 15 mg. daily when testosterone was dissolved in propylene glycol and absorbed sublingually and matched the good

effects of 30 mg. perorally. In this patient linguet therapy constituted a notably economic method.

In *case 4*, the patient, another typical eunuchoid, derived equivalent maintenance benefit from only one 5-mg. linguet of methyl testosterone as compared to the need of 15 mg. daily when testosterone dissolved in propylene glycol was administered sublingually, and the results equaled those obtained previously from 30 mg. daily perorally; again a remarkable saving in medication.

In *case 5*, the patient had been greatly improved and well maintained on 12.5 mg. daily of free testosterone dissolved in propylene glycol and absorbed sublingually. Equally excellent results were obtained by one 5-mg. linguet of methyl testosterone daily; again an appreciable saving of material.

In *case 6*, the patient had been satisfactorily maintained on one 10-mg. tablet perorally, and likewise on 10-mg. daily absorbed sublingually (free testosterone dissolved in propylene glycol). One 5-mg. linguet daily accomplished the same purpose.

In *case 7*, prior to coming under our observation, the patient had been greatly improved by injections twice a week of 25 mg. of testosterone propionate plus 20 mg. of methyl testosterone daily three times a week perorally. He had been without any treatment for 9 months when we instituted therapy with methyl testosterone linguets. Only three 5-mg. linguets, 15 mg. daily, were required to obtain further improvement (fig. 2, *B* and *C*).

In *case 8*, a lad almost 20 years old who had suffered destruction of both testes from orchitis, one side at 13 years of age, the other at 16.5 years, had matured partially during the interim. He received testosterone propionate parentally for 3 months when 18 years of age, but this therapy had to be discontinued for economic reasons. He had been untreated for 10 months when therapy with methyl testosterone linguets was instituted in a dosage of 15 mg. daily. This amount produced a gain of 21 lb. in body weight in 10 weeks.

In *case 9*, the patient, a characteristic example of severe pre-adolescent eunuchoidism, had never received any form of testosterone treatment. Therapy with methyl testosterone linguets was begun Nov. 12, 1942, and at the time of this report, 3.5 months later, he had gained 25.5 lb., erections were occurring 2 to 3 times daily, and the penis and scrotum, as is apparent in the photographs (fig. 3, *C* and *D*) had developed strikingly. This remarkable result was accomplished with but 3 linguets, 15 mg. daily. In view of reports such as that of Eidelsberg and Madoff (14) that as much as 100 to 150 mg. daily of methyl testosterone orally was necessary to produce similar improvement, it is clear that therapy with methyl testosterone linguets constitutes a very substantial saving.

In *case 10*, which represents an extraordinary instance of severe sexual retardation at the advanced age of 43 years, the patient received 100 mg. daily of methyl testosterone perorally for 4.5 months. Gratifying improvement is obvious from the photographs (fig. 4, *C* and *D*). To determine what dosage of methyl testosterone linguets would maintain and perhaps further this improvement, an initial amount of 5 linguets, 25 mg. daily, was tried. Two weeks later this was reduced to 15 mg. daily; 2 months later to 10 mg. daily; and 5 weeks later to but 5 mg. daily. The photograph (fig. 4, *E*) reveals that despite the sharp curtailment in dosage, the penis had enlarged appreciably and pubic hair had continued to grow. On this relatively tiny dose erections decreased in frequency, but there was no loss of strength and energy and the patient expressed himself as quite content. Here again an amazingly small dose proved satisfactory.

In *case 11*, the patient, a 73-year-old-man was castrated a year before because of trauma to the testes and had suffered severely from the climacteric symptoms of frequent hot flushes, melancholia, emotional instability with weeping spells and marked diminution in mental vigor and initiative. He received a total of 5 injections of testosterone propionate, given once a week. However, the climacteric symptoms recurred before the week had elapsed between injections. One to two 5-mg. linguets of methyl testosterone daily completely controlled the above symptoms and his mental alertness returned sufficiently to enable him to resume in-

tensive reading and writing (as an author). Here again a remarkably small dose was entirely satisfactory despite castration.

Case 12 is that of a young acromegalic who suffered from secondary hypogonadism with complete loss of libido and potentia. Testosterone propionate, parenterally, 25 mg. three times a week for 3 months, restored his sexual vigor completely. Subsequently, this improvement was maintained by three 5-mg. linguets of methyl testosterone daily.

SUMMARY

Twelve males, whose ages ranged from 19 to 73 years, were victims of severe hypogonadism. Nine of these 12 patients had never matured; one had matured partially; one suffered from testicular deficiency secondary to acromegaly; one had been castrated at 72 years of age. Some of these patients had been treated previously by other modes of testosterone therapy. All were well maintained on much smaller amounts of testosterone compounds when methyl testosterone was administered in the form of 5-mg. linguets designed for sublingual absorption. In 6 of the 12 patients, one 5-mg. linguet daily sufficed for maintenance a remarkably small dose. Only 15 mg. daily of methyl testosterone in linguets produced striking genital improvement in a 19-year-old lad suffering from severe eunuchoidism and who had never had any other form of testosterone therapy. He gained 25.5 lb. in 3.5 months.

Methyl testosterone linguets in the form of 5-mg. hard compressed tablets for sublingual absorption, is to date, by far the most economical mode of administering androgens to hypogonad males. These linguets dissolve, and therefore absorb, slowly, about 15 to 30 minutes being required; patients do not find them unpleasant.

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Effect of Injections of Testosterone Propionate on a Male Subject with Nephrotic Syndrome[1]

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DURING the active phase of the chronic nephrotic syndrome loss of protein in the urine is a factor in lowering the plasma proteins to the edema level (1). Another possibile cause is partial failure of albumin production (2). Careful attention to dietary protein and caloric intake, when supplemented by judicious restriction of salt and water, may do much to improve general nutrition (3–6) and control edema. Such measures are not very effective in maintaining an adequate level of plasma albumin but do offset serious inroads on tissue proteins.

In seeking for more active stimulation of the protein anabolism of these individuals, one's attention is naturally drawn to certain remarkable effects of some of the androgenic steroids. It is now a well-established fact that testosterone acetate or propionate will cause retention of considerable amounts of nitrogen in the dog (7,8) and also in man (9–12). In some experiments of our own (unpublished data) this effect has continued for as long as 80 days and the retention of nitrogen has been much greater than could be accounted for on the basis of hypertrophy of genital tissues. There are, in addition to nitrogen retention, renal changes noted, particularly in the mouse (13,14,15) and also reported in the rat (16,17,18). The renal tubular epithelium hypertrophies and the kidneys increase in weight in the mouse. Welsh *et al.*, (19) found the diodrast T_m of young female dogs increased by as much as 100 per cent when large doses of testosterone propionate were injected. Selye (20) thought that administration of testosterone afforded partial protection to the kidneys of mice poisoned with bichloride of mercury. The suggestion that this form of hormonal therapy might prove beneficial in human renal disease has been made several times (16,20,21). At present it seems to have been tried but once and with negative results (18).

Although anatomical changes in the tubules are characteristic of the nephrotic state, and the usual tests of glomerular function are but moderately impaired, it would seem that serious lesions of the glomerular filter must exist, otherwise proteins should not pass freely into the urine. From what is known of the effect of androgens on the kidney, one would be led to surmise, then, that they would not materially affect proteinuria unless indirectly by increasing the efficiency with which dietary protein was used to synthesize plasma protein. However, except in regard to nitrogen-retaining properties, there is little point in comparing the human and animal experiments, for the dosage that has been used to produce renal hypertrophy in animals is enormously greater on a per kg. basis than has been given to man.

The following case report deals with our experience in the treatment of the nephrotic state with testosterone propionate.

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CASE HISTORY

A male, aged 24 years, was well until January, 1941, when he had a rather protracted respiratory infection consisting of sore throat, laryngitis and bronchitis. On recovery he felt well until June, 1941. The onset of symptoms at this time was insidious with weakness, mild anemia and swelling of ankles. The urine was found to contain large amounts of protein and many hyalin and granular casts with never more than an occasional erythrocyte. *Blood:* R.B.C. 4.1 million/cu. mm.; Hb., 13.4 gm. per 100 cc. *Serum:* Total protein, 4.1 gm. per 100 cc.; albumin, 1.2 gm.; globulin 2.9 gm.; nonprotein nitrogen, 38 mg. per cent; calcium, 7.1 mg. per cent; inorganic phosphorus, 4.6 mg. per cent. The serum was intensely lipemic at all times.

Plasma Lipid

Total lipid	2201 mg. per cent
Phospholipid	464 mg. per cent
Total cholesterol	977 mg. per cent

Urea Clearance

Date	*Clearance*
7/23/41	Standard 60 per cent of normal
5/25/42	Standard 30 per cent of normal (Followed streptococcal cellulitis)
9/22/42	Maximum 69 per cent of normal
10/13/42	Standard 56 per cent of normal
2/ 1/43	Standard 48 per cent of normal
2/11/43	Standard 45 per cent of normal
3/ 4/43	Standard 46 per cent of normal

The patient's course was characterized by moderate edema at all times interspersed with episodes of severe generalized anasarca. One of the latter was observed on the metabolic service and appeared to have been due to marked increase in proteinuria following extraction of an infected tooth combined with simultaneous restriction of protein in the diet. In May, 1942, anasarca disappeared rapidly with a loss of 23 kg. in weight following a cellulitis of the leg due to infection with hemolytic streptococcus. Proteinuria decreased markedly and the albumin fraction of the serum protein rose to 2.9 gm. per 100 cc. As noted above, the urea clearance reached its lowest level at that time. Three months later, renal function, as measured by the urea clearance, had improved; proteinuria was again extremely high; the serum albumin lower; and the edema was increasing.

Metabolic study

The period of observation on testosterone propionate was one in which the patient was free from complicating illness and was able to cooperate fully.

Method. The subject lived on the metabolic ward where he received a constant and carefully weighed diet of 3170 calories and 125 gm. of protein per diem. The nitrogen content of the diet was determined by macro-Kjeldahl analysis of composite samples of the daily food. Urine was collected in 24-hr. periods and analyzed for total nitrogen and total protein. Feces were marked with carmine and pooled in 5-day periods before analyses were made for nitrogen. Nitrogen balance was computed every 5 days. Vena punctures were performed without stasis in the morning, about 14 hours after the last previous meal and while the patient was still recumbent. Serum proteins were determined by the method of Howe.

Salt intake was estimated to be 2.5 to 3 gm. a day; liquids in the diet including drinking water were restricted to 1100 cc./day. The first three periods, *8* to *10*, and the last six, *19* to *24*, served as controls. Injections of testosterone propionate[2] were given intramuscularly in *periods 11* to *18*. The dose of hormone was 25 mg./day for 15 days, was increased to 50 mg./day for 15 days and then reduced to the initial level of 25 mg./day for 10 days. The total dose was 1375 mg. in 40 days.

RESULTS

Tabular and graphic presentations of the data appear in tables 1 and 2 and figure 1.

Pre-treatment control period. The subject was in moderately positive nitrogen balance during the preliminary control *periods 8* to *10*. During a previous admission, with a slightly lower protein intake, it had been impossible to prevent accumulation of edema without the administration of ammonium chloride and this was given in doses of 8 grams per day during *periods 8* and *9*. A diuresis resulted, accompanied by rather rapidly increasing proteinuria (22) and weight loss. With omission of the ammonium chloride in *period 10* the proteinuria decreased and both this and the weight reached a fairly constant state.

Testosterone treatment periods. a) Nitrogen retention was above that of control periods due to injections of testosterone propionate in *periods 11* to *18*. The maximum effect was observed at the dosage level of 50 mg./day but the gain over that of 25 mg./day was small. The peak of retention appeared in *period 15*

[2] Dr. E. Oppenheimer of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, supplied the testosterone propionate (Perandren) used in this work.

TABLE 1. METABOLIC STUDY OF MALE SUBJECT WITH NEPHROTIC SYNDROME BEFORE, DURING AND AFTER TREATMENT WITH TESTOSTERONE PROPIONATE

Periods 5-Days	Nitrogen Balance	Urine Protein	Creatine	Creatinine	Testosterone Propionate	Body Weight
	gm.	*gm.*	*gm.*	*gm.*	*mg.*	*lb.*
8	+ 9.78	115.68	0.91	9.01		772.6
9	+ 7.24	154.00	1.17	8.59		73.55
10	+10.37	123.75	1.20	8.36		76.18
11	+16.83	142.60	0.69	8.64	125	77.31
12	+16.37	151.30	0.88	9.11	125	78.93
13	+17.92	151.10	0.82	8.48	125	80.29
14	+20.71	149.60	0.78	9.61	250	81.55
15	+20.24	146.90	0.74	9.25	250	83.16
16	+17.10	157.50	1.32	9.08	250	84.01
17	+16.23	159.40	1.11	9.50	125	84.40
18	+15.13	141.20	1.24	9.76	125	85.01
19	+10.04	165.30	0.97	10.20		84 72
20	+ 3.33	177.60	1.29	10.07		83.51
21	+ 3.92	157.30	1.15	9.49		84.16
22	+ 7.39	129.80	1.07	11.44		82.45
23	+16.36	123.25	1.17	9 93		78 06
24	+11.88	119.50	1.13	9.91		75.38
						74.11

and thereafter the nitrogen retaining effect of the hormone seemed to decline slowly. There was a 'rebound' in urinary nitrogen when the hormone was withdrawn, but not of sufficient magnitude to produce a negative nitrogen balance. The average nitrogen retention per diem of control *periods 8* to *10* and *23* to *24* was 2.22 gm. The mean nitrogen retention in the periods of treatment with testosterone was 1.29 gm./day higher.

b) Proteinuria was exceptionally high at all times. There were many days during which the urinary protein was more concentrated than the protein of the serum. The increased proteinuria of *period 9* was probably caused by the action of the ammonium chloride (22). The highest values for urinary protein were found in the periods immediately following discontinuance of testosterone (*periods 19–21*). In neither instance was there any clear relationship between the amount of protein excreted and the volume of the urine. As mentioned in paragraph *a*), the periods considered to be free from testosterone effects were *8* to *10* and *23* to *24*. The mean proteinuria of these periods was less by 4.6 gm./day than that of the testosterone treatment periods (*11–18*). The increase in the latter, while not very great, has a probability of more than 100:1 of being real and not a purely chance observation.

c) *Gain in weight.* The increase in weight directly associated with therapy was 7.8 kg. Some of this was quite obviously the result of increasing edema. From the nitrogen balance (*periods 11–18*), one may estimate that 4.1 kg. was presumably muscle tissue. The remaining 3.7 kg. was extracellular water. Subjectively, the patient felt stronger in spite of increasing edema, an observation directly opposed to his usual reaction when gaining rapidly in weight.

If the entire retention of nitrogen of the 85 experimental days is taken into account, one may calculate a gain in muscle tissue of 6.5 kg. This was completely obscured by the diuresis and loss of edema fluid which took place in *periods 21* to *24*.

d) The urea clearance did not change significantly during the periods of treatment.

e) Creatinuria was present in moderate degree and decreased somewhat during the first five periods of treatment.

Post-testosterone treatment period. The most interesting feature of this phase was the onset

TABLE 2. PROTEIN METABOLISM IN MALE SUBJECT WITH NEPHROTIC SYNDROME

Control Periods 8 to 10 and 23 to 24 (25 days)		
Protein intake from food		3125 gm.
Protein lost in urine	636 gm.	
Protein deposited as tissue	347 gm.	
Sum of urine and tissue protein	983 gm.	983 gm.
Balance catabolized		2142 gm.
Dietary protein converted to body protein		31.5%
Dietary protein wasted as urine protein		20.3%
Testosterone treatment periods 11 to 18 (40 days)		
Protein intake from food		5000 gm.
Protein lost in urine	1200 gm.	
Protein deposited as tissue	878 gm.	
Sum of urine and tissue protein	2078 gm.	2078 gm.
Balance catabolized		2922 gm.
Dietary protein converted to body protein		41.5%
Dietary protein wasted as urine protein		24.0%
Entire experimental period (85 days)		
Protein intake from food		10,625 gm.
Protein lost in urine	2589 gm.	
Protein deposited as tissue	1377 gm.	
Sum of urine and tissue protein	3966 gm.	3966 gm.
Balance catabolized		6659 gm.
Dietary protein converted to body protein		36.7%
Dietary protein wasted as urine protein		24.3%

of a prolonged diuresis and a loss of 10 kg. in weight which began about 12 days after the hormone treatment was stopped. We would like to think that the following factors were contributory: *a*) A small but definite rise in serum protein from 3.0 to 3.8 gm./100 cc. *b*) Withdrawal of the salt and water-retaining effect of testosterone. *c*) Repair of depleted tissue protein, 'increased tissue turgor.' On the other hand, such periods of diuresis have been observed in this type of patient without any demonstrable cause and this fact must be kept in mind in the assessment of any therapeutic results.

DISCUSSION

It is evident that testosterone propionate exerts its usual anabolic effect on protein metabolism in the nephrotic subject. Pretreatment determinations of the excretion of 17-ketosteroids by our patient were made but were not considered very accurate due to the high concentration of urinary protein. Values of 14 to 15 mg. per day were obtained and appear to indicate an adequate production of natural androgens.

Utilization of dietary protein to build body protein. The ability of the patient to tolerate an extremely severe proteinuria and deposit protein in his tissues simultaneously indicates fairly efficient utilization of dietary protein. This is revealed in the summary of the protein metabolism in table 2.

The chief disadvantage to this form of therapy, but not a serious obstacle in the present instance, was its effect on retention of salt and water. Kenyon (9, 10, 12) has noted the electrolyte-retaining action of the hormone in man on several occasions. Its behavior in this respect appears to be exaggerated in nephrosis and might prove to be a source of embarrassment in a patient who was already seriously edematous.

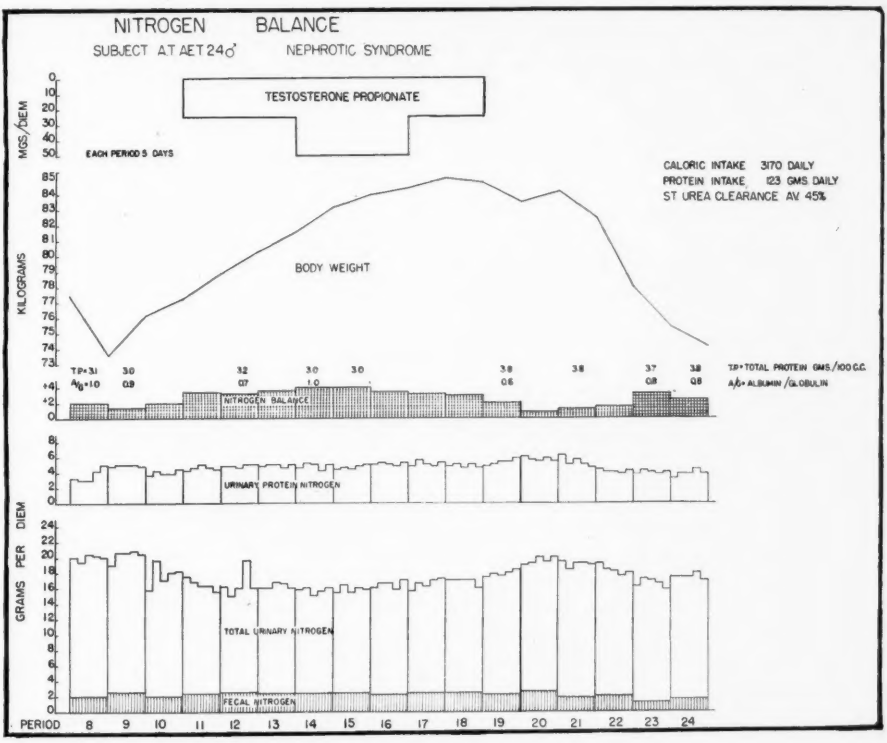

FIG. 1. Effect of injections of testosterone propionate on nitrogen balance, urinary protein nitrogen and body weight.

The conversion of dietary protein to body protein (tissue and urine protein) was remarkably good and achieved the rather high level of 41.5 per cent of the intake in the periods of treatment with testosterone. Of the extra nitrogen utilized for formation of protein in these periods, about half seems to have contributed to a more intense proteinuria while the remainder was retained in the body. Both the increase in proteinuria and the small rise in concentration of serum protein suggest some increase in the synthesis of plasma proteins. More evidence on this point is required, however, in view of the rapid and sometimes inexplicable variations that occur in the urinary and plasma proteins of the nephrotic.

SUMMARY

An anabolic effect of injections of testosterone propionate on the protein metabolism of a nephrotic subject has been demonstrated. The hormone increases the rate of deposition of protein in the tissues and appears to augment proteinuria slightly. There is likewise a distinct tendency for edema to increase during the period of injections, presumably due to retention of salt and water.

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Endocrine Treatment of Enuresis

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Enuresis in the child is a condition which may have organic or psychogenic factors as a cause. The organic cause may be purely local and may consist of some palpable physical irritating stimulus, such as inflammatory conditions in the genito-urinary tract. It may be of a general physical nature such as great debility from nutritional causes or following severe illnesses. There may be endocrine dysharmony with its influence on neuromuscular function. It may be entirely neurogenic due to organic disease and dysfunction or aplasia either central or local, of nerve structures which innervate the bladder. The cause may be entirely psychogenic. The hypersensitive neurolabile child with great neuro-instability or the psychopathic child with behavior complexes presents this type of case. Many believe that this type of etiology is predominant in all enuretics. The enuretic is an individual whose neuro-muscular micturition mechanism is not normally stabilized. Many factors which do not affect the normal child act as adverse stimuli in the susceptible incontinent child.

Ederer and Lederer (1) believe that in all enuretics in whom the etiology is not on an organic or anatomic basis, loss or dislocation of a conditioned reflex is the real cause of the enuresis, and is of central nervous system origin. Excitability of the cortical cells is either decreased or that of the sub-cortical cells is increased, or both factors may be present. It is of course conceivable that in this concept of the etiology all kinds of local or environmental factors may contribute to the development of the central disorder.

The treatment of the condition is shaped largely according to the predominant etiological factor and basically aims at the re-establishment and proper synchronization of the conditioned reflex. The desire to urinate must chronologically synchronize and coincide with the conscious action of the bladder sphincter-closing mechanism. Restriction of fluid intake, dietary changes and environmental changes which will influence and improve both the physical state and the psyche of the child are important curative measures. Re-education and re-establishment of an adequate conditioned reflex are the goal of any form of treatment.

Of a large list of drugs used the most useful have been atropine and the belladonna preparations. Recently ephedrine has been quite extensively used, not to control the enuresis, but to prevent the deep sleep which is often characteristic of the chronic enuretic, thus allowing him to waken when the pressure in the bladder prompts the desire to urinate; this in turn initiates the conditioned reflex which sets in motion the mechanism of sphincter control.

The extensive research in the past decade or two in the field of endocrinology, the isolation of individual hormones, and discovery of their potent effects particularly on the sex glands and the sex organs, has led to some interesting observations and therapeutic experiences. The question has frequently been raised whether endocrine influences are not, among other things, a factor in the development of enuresis —the theory being advanced that immaturity of the genital structures and organs both as to muscular structure and urine control could be at fault. This view has been strengthened by some clinical reports which have appeared from time to time and which showed that the use of various endocrine substances seemed to have a

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definite effect in controlling or relieving the disorder.

Cain (2,3) used anterior pituitary products given orally and claimed good results for them in cases of incontinence. Nittis (4) found such preparations useful and effective in the treatment of enuresis in children. He proposes the acceptance of the theory that lack of maturation of the structures of the genito-urinary region is responsible for much of the nocturnal incontinence in many children and that the use of endocrine substances which are known to produce precocious maturity of the genital organs will prove beneficial. Malavozos (5), believing the underlying cause of enuresis to be immaturity of the genito-urinary organs, treated the condition with anterior pituitary substances with good result. Later he and Goldman (6) attempted to determine whether the follicle-stimulating or the luteinizing factor is responsible for the result and reached the conclusion that the best results are obtained only when both substances are given in fairly large doses. Huffman (7), accepting the theory that in most cases of nocturnal urinary incontinence in children the underlying cause is some form of immaturity of the structures responsible for micturition, and noticing the fact that the administration of anterior pituitary-like substances in most cases results in overgrowth of the external genitalia and premature puberty, gave such substances to a small group of children suffering from nocturnal enuresis. The ages of the children ranged from 5 to 9 years. In none of the children was there any frank anatomic defect. A commercial preparation of anterior-pituitary-like substance containing 500 international rat units per cc. was used. Injections were given two or three times weekly. In all of the cases appreciable improvement of the condition was noted within the second week of treatment and complete relief was observed in all cases before the end of the fourth week. The result of the treatment was prompt and spectacular and in no case were visible anatomic changes noted. Since the period of administration of the gonadotropic substance was of such short duration, no external signs of premature puberty were anticipated and none occurred. According to this author's concept, incontinence is not a physiologic condition occurring at a certain age and its abolition does not come about through the establishment of precocious maturity of certain structures, but rather through the further development or maturation of these structures to a stage corresponding to the child's age.

Male sex hormones in the form of testosterone propionate were used by Bodechtal (8) and by Zehn (9) in the treatment of incontinence in adult males suffering from prostatic disorders and females who were nearing the menopause. These authors report strikingly favorable results and attributed them mainly to improved tonus of the bladder muscle produced by the use of this preparation. Zehn also used this preparation in the treatment of a number of children afflicted with nocturnal or nocturnal and diurnal enuresis. Daily injections in dosages up to 5 mg. were given for a short period, followed by injections given at intervals of 2 or 3 days. No other form of treatment was given to any of the cases. The results were excellent, in practically no case was there a failure, and in some the therapeutic result was quite spectacular.

CLINICAL PROCEDURE

Fifty children with enuresis were treated with male sex hormone preparations. Forty-six wet nightly or several times a night and 3 had both nocturnal and diurnal enuresis. None showed any sign of mental retardation. Of the 50 cases, 36 were boys and 14 girls. They were divided into two age groups; those 3.5 to 6 years and those 7 to 14 years of age. The first group comprised 17 boys and 7 girls. The second, 19 boys and 7 girls.

Methyl testosterone was given once daily, or twice in refractive cases, a dosage of from 10 to 20 mg. daily, which was continued for several weeks and then reduced or given less frequently after definite improvement or cure of the case. The intramuscular injections of the propionic ester of testosterone in oil was given once daily in a dosage of 10 or 25 mg. Testosterone in the form of a topical application was applied twice daily on the lower part of the abdomen, using about 8 mg. each day. After improvement or cure of the patient, the preparation was applied once daily and continued for about two months. Ten boys and 4 girls were treated in

this way. In 26 boys and 9 girls the male hormone was given orally and in one girl who had not responded to inunction or oral treatment, the preparation was given by intramuscular injection. In few cases was treatment continued beyond two months.

No other form of treatment except a restriction of fluid and a high salt intake was used. No other drugs were given. Except for some correction of gross environmental defects, no form of psychiatric treatment of the case was attempted. Careful dietary management along with fluid intake restriction was practiced in every case, and the child was awakened and made to pass urine in the early part of the night.

RESULTS

The therapeutic results in the total of 36 boys showed 20 entirely cured, 11 improved and 5 unchanged in condition. Of the 14 girls 7 were entirely cured, 6 improved and one showed no change. The boys seemed to respond to the treatment more quickly than did the girls. In 13 of the completely cured cases the results with the treatment were prompt, occurring in less than 2 weeks.

In a few of the cases occasional wetting reoccurred when the treatment was stopped but immediately ceased when treatment with testosterone propionate was resumed. Very few of the completely cured or markedly improved cases required treatment beyond two months. One case required treatment for one year before the enuresis stopped entirely.

DISCUSSION

In those children which showed no improvement there were, in practically every case, factors which no doubt contributed to the poor result. The mothers often admitted that they did not give the preparation regularly, or often, in the case of the older child they left the entire management of the treatment, such as fluid intake restriction and high salt intake and the medication to the child itself. These were, without exception the cases which responded poorly or showed no improvement at all.

It may be questioned whether the fluid intake restriction, the high salt intake and getting the child up in the early part of the night might not in itself have been a major contributing factor in the cure or improvement and that the hormone treatment was really not the principal effective agent. That this was not the case is apparent since nearly all of the patients reported had been more or less and for long periods of time on this type of management, including the use of belladonna preparations, and had shown no improvement. The relapse of some of the cases when hormone treatment was stopped, and the prompt relief or improvement in the enuresis when treatment was resumed is further proof that the principal effect was probably due to the drug.

SUMMARY

The net result of treatment with male sex hormone in the 50 cases of enuresis in children shows 54 per cent completely cured, 34 per cent much improved and in 16 per cent there was no improvement or complete failure. This percentage could no doubt have been improved had there been better and more careful control and management of the case.

The effect in some cases was quite dramatic and far more rapid than can be achieved with more general forms of treatment or the purely psychiatric approach to the problem. We are quite convinced that the use of male sex hormone preparations in moderate dosage, even if given over long periods of time in this age group, produces no lasting undesirable effects such as sexual precocity or unusual permanent enlargement of the sex organs.

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Hyperparathyroidism: A Report and an Analysis of 13 Cases Occurring in the Middle Western States

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IT IS generally believed that there is a specific geographical distribution for hyperparathyroidism and that the disease is extremely rare in the middle western part of the United States. Wilder and Howell (1) suggested that vitamin D, the deficiency of which has been considered as an etiologic factor, was probably one of the causes for the disease being so extremely rare in this part of the country. The occurrence of 13 proven cases at the University Hospitals in Iowa City during the past 12 years casts some doubt regarding the rarity of this disease in the middlewestern states. It appears pertinent, therefore, to call attention to the occurrence of these cases, to analyze their manifestations, ascertain which of the manifestations led to the disease being suspected, and to discuss some of the diagnostic difficulties.

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Analysis of Cases

The ages of the 13 patients varied from 20 to 60 years. Twelve were white and one was a negro. The sexes were about equally represented. Of these patients, 11 lived in Iowa, 1 in Ohio, and 1 in Illinois. They all had lived in the middle west for 20 years or longer. The birthplaces were as follows: 7, Iowa; 1, Sweden; 1, Nebraska; 1, Oklahoma; 1, Pennsylvania; 1, New York; and 1, Russia. The occupations were as follows: 7, housewives; 1, clerk; 1, machinist; 1, blacksmith; 1, farmer; 1, teacher, and 1 had no occupation. The symptoms began from 4 months to 13 years before admission and the initial symptoms are shown in table 1. It will be noted that pains and aches in the

TABLE 1. INITIAL SYMPTOMS AND DURATION OF HYPERPARATHYROIDISM IN 13 CASES IN THE MIDDLE WESTERN STATES

Case	Weakness	Gastrointestinal	Presence of Pains and Aches of Muscles and Joints	Pain in Back	Pathologic Fracture	Bone Cyst	Genitourinary Symptoms	Duration, yr.
1								5
2			none		occurred			1/3
3				present	occurred			7
4	present				occurred	present		4
5	present	present					present	6
6	present	present						13
7	present	present		present			present	5
8						present		1/3
9			none				present	12
10			none			present		4
11				present				5/12
12			none	present				1
13	present			present	occurred	present	present	3

TABLE 2. SUBJECTIVE MANIFESTATIONS IN 13 CASES OF HYPERPARATHYROIDISM AT TIME OF HOSPITAL ADMISSION

	Muscle and Joint Aches and Pains	Weight Loss	Mass in Neck	Decrease Stature	Pathologic Fracture	Local Swelling	Genito-Urinary Symptoms	Gastro-Intestinal Symptoms	Cardiac Respiratory Symptoms
Present	12	8	4	7	4	7	7	8	6
Absent	1	2	9	4	9	6	6	5	7
Questionable	0	3	0	2	0	0	0	0	0

muscles and joints were the most common initial symptoms, in fact they were the predominating symptoms in 7 of the cases. These pains are aching and boring in character, but frequently the patient is unable to describe them. They are usually located in the lower extremities and lower back, but in 3 of our cases they were present also in the shoulders and arms. There are no local objective manifestations, as a rule, but in 2 cases there was enlargement of the knee and elbow joints, respectively, and 1 patient had a history of generalized migratory swelling of the joints of the upper and lower extremities shortly before admission.

Pathological fracture was one of the initial symptoms in 4 cases. In 3 of these vague muscular aches and pains had been noted for indefinite periods previous to the fracture, but they were not of sufficient intensity to demand attention. In one case, however, the pathological fracture was the only symptom that was present.

Localized swelling surrounding a bone cyst was the initial abnormality noted in 3 cases. Of these, 2 had noted muscular and joint aches and pains previously and the appearance of localized swelling of the cyst caused them to seek aid. In one case, however, the deformity of the cyst was the only symptom experienced by the patient.

Genito-urinary symptoms such as dysuria, urgency and frequency were among the initial subjective manifestations in 3 instances. In 2 of these cases the genito-urinary symptoms were the outstanding initial ones, but later they were over-shadowed by the muscular and joint pains. Symptoms had been present in 8 of the cases for 4 years or longer.

The subjective manifestations present at admission are shown in table 2. It is to be noted that muscular and joint aches and pains were the most constant, being present in 12 of the 13 cases. Gastroenteric symptoms and loss of weight occurred in over one-half of the cases. Symptoms referable to the cardio-respiratory and genito-urinary systems, decrease in stature and localized swelling due to bone cysts were present in about one-half of the cases.

The objective manifestations are shown in table 3. It will be noted that there were renal stones in 8 instances and bone cysts in 7 cases. The cysts were present in the mandible only in 2 cases and the teeth were abnormal in 5. The serum calcium was elevated in 10 cases and the phosphorus was diminished in 11. The serum proteins were decreased, however, in 4 cases.

Analysis of the records to ascertain which of the manifestations led to the suspicion of the disease is of interest. In 7 instances muscular aches and joint pains led to further investigation of the patient. In 4 of these the possibility of hyperparathyroidism was not apparently suspected until after roentgenograms revealed bony changes consistent with the disease. In 3 others, however, the disease was suspected before the roentgenograms were made. The data are shown in table 4. Pathological fractures led to further study in 3 cases, calcium deposits in the fingers in 1 case, cyst of the jaw

TABLE 3. OBJECTIVE MANIFESTATIONS OF HYPERTHYROIDISM IN 13 CASES

	Renal Stones	Cysts Jaw	Other Bone Cysts (by X-ray)	Abnormal Teeth	Elevated Serum Ca	Decreased Serum P	Low Serum Protein	Elevated Serum Phosphatase
Absent	4	9	6	7	3	2	3	5
Present	8	4	7	6	10	11	4	6
Questionable	1	0	0	0	0	0	0	0

in 1, and dysuria in 1 case. Confirmation of the diagnosis in these cases is shown in table 5. It is to be noted that abnormal parathyroid glands were discovered in 12 cases at operation and in 1 at postmortem examination. Of these, ful cases the elevated phosphatase and an increased urinary calcium were of value. Five cases were of particular interest. Case 3, a woman, aged 28 years, was observed on several occasions between 1934 and 1941 because of

TABLE 4. SUBJECTIVE SYMPTOMS LEADING TO SUSPICION OF HYPERPARATHYROIDISM OR TO FURTHER CASE STUDY AND OBJECTIVE MANIFESTATIONS IN EACH OF THESE

Case	Subjective Symptoms	Objective Manifestations		
		Roentgenograms	Serum Ca	Serum Phosphorus
1	Muscular and joint aches and pains	Bone cysts	Elevated	Decreased
2	Muscular and joint aches and pains	Osteoporosis and cysts	Elevated	Decreased
3	Path. fracture	Osteoporosis and cysts	Normal	Normal
4	Path. fracture	Osteoporosis and cysts	Elevated	Decreased
5	Calcium deposits in fingers	Osteoporosis	Elevated	Elevated
6	Muscle and joint aches and pains	Bone cysts	Elevated	Decreased
7	Muscular and joint aches and pains	Osteoporosis and cysts	Elevated	Decreased
8	Swelling of jaw	Osteoporosis and cysts	Elevated	Decreased
9	Dysuria	Renal stones	Normal	Decreased
10	Muscle and joint aches and pains	Bone cysts	Elevated	Normal
11	Muscle and joint aches and pains	Normal	Elevated	Decreased
12	Muscle-joint aches and pains and swelling of jaw	Bone cysts	Normal	Normal
13	Muscle pains; path. fract.	Bone cyst	Elevated	Decreased

11 were adenoma and 2 were hyperplastic glands. The latter cases are of interest. Case 3 showed very slight improvement 3½ months after operation and in the other case the gland was found at autopsy. One patient, case 13, died 2 days after operation in apparent cardiac failure. The other 10 patients showed definite improvement.

The diagnosis was not difficult to establish in most cases once it was suspected. The elevated serum calcium and diminished phosphorus were of aid in most instances. In doubt-

TABLE 5. PATHOLOGIC REPORT AND RESULT OF OPERATION IN 12 CASES OF HYPERPARATHYROIDISM[1]

Case	Pathological Report	Result of Operation
1	Adenoma	Improved
2	Adenoma	Improved
3	Hyperplasia	Very slight improvement in 3½ months
4	Adenoma	Improved
6	Adenoma	Improved
7	Adenoma	Improved
8	Adenoma	Improved
9	Adenoma	Improved
10	Adenoma	Improved
11	Adenoma	Improved
12	Adenoma	Improved
13	Adenoma	Died

[1] Case 5 was not operated. Autopsy revealed hyperplasia of parathyroids.

pathological fractures and bony changes characteristic of hyperparathyroidism. The serum calcium, phosphorus and proteins, and the urinary calcium were consistently normal. The phosphatase was elevated on all occasions and the urinary phosphorus on 2 occasions. The parathyroid gland removed at operation was hyperplastic and the improvement of the patient was questionable. Case 6, a negro woman, aged 52 years, had symptoms for 9 years. During the first admission to the hospital the disease was not suspected. On the second admission 6 years later, however, the disease was suspected but the serum calcium and proteins were within normal limits; the phosphorus, however, was diminished. Two months later the serum calcium and phosphatase were elevated and phosphorus was decreased. At this admission she refused operation and returned 9 months later. The serum calcium was 13.2 mg., phosphorus, 1.9 mg., but the phosphatase was normal. Urinary calcium estimations during this admission were found to be increased. Case 12, a white woman, aged 60 years, was found to have a bone cyst and the serum calcium varied between 10.2 and 12.0 mg., phosphorus between 4.0 and 5.1 mg., and the urinary calcium and phosphorus were normal. The serum proteins were normal.

yet an adenoma of the parathyroid was removed and she improved. Case 5, a white male, aged 30 years, had calcium deposits in the fingers and elevated serum phosphorus. This case was reported in detail by Curtis and Feller (2) and was due, undoubtedly, to hyperplasia of the parathyroid, secondary to longstanding extensive renal pathology. Case 9, a white female, aged 47 years, had only urinary symptoms; renal calculi were present. She had had a known hypertension for 17 years. The serum calcium, phosphorus and proteins were normal and an adenoma of the parathyroid was removed. It is not known whether or not hyperplasia of the parathyroid gland was secondary to the renal pathology. Failure to find the offending gland during exploration of the neck does not exclude the diagnosis of hyperparathyroidism. One of our cases was explored three times by excellent surgeons before the gland was discovered and removed from the substernal space.

DISCUSSION

Inquiry among men from large medical centers in the middle west reveals that cases of hyperparathyroidism are extremely rare in their clinics. Some of these men were among the first to report cases of this disease. It certainly cannot be said that they are unaware of the manifestations of the disease and it is extremely unlikely that the disease is overlooked in patients observed by them. Why then are we observing more of these cases than other clinics in the midwest? The answer, of course, is not known. The years in which our cases were observed are of interest. One was diagnosed in 1929, 2 in 1935, 1 in 1937, 4 in 1938, 1 in 1939, 1 in 1940, and 3 in 1941. These figures show that 9 of our cases have been observed during the last 4 years. This would indicate that we were becoming more conscious of the disease or that the incidence of the disease was increasing.

The possibility that vitamin D deficiency was a factor in the etiology of these 13 cases appears somewhat remote. Of the 7 housewives, 4 lived in rural communities and of the remaining 6 patients, 4 had led active outdoor lives. Special studies for vitamin A deficiency were made in 4 cases. Of these, 3 showed no evidence of vitamin deficiency and 1 was considered to be borderline. Albright's (3) argument against the disease being a vitamin D deficiency brings out that the disease is rare in the negro. It is of interest that one of our patients was a negress who was fairly dark.

The diagnosis of the disease is usually relatively easy once it is suspected. The association of the bone lesions is so widely appreciated that they need no comment. Most of our cases exhibited bone lesions which aroused suspicion of the disease. In one case, however, the symptomatology suggested the disease and the diagnosis was established and proven without there being evidence of bone lesions. Albright (3) states that "it is of interest that no proven case has been published from any other clinic other than the Mass. Gen. Hospital in which no bone disease was present and which was diagnosed during life." The association of renal calculi with hyperparathyroidism has also been emphasized. Of our cases, 8 exhibited renal stones, but in only one, Case 9, was the urinary symptoms of sufficient intensity to cause the patient to be admitted to the urology service of the hospital. This is of interest in view of the fact that Dr. Flocks of the Urology Department has been so intensely interested in renal stones and has been acutely aware of hyperparathyroidism as an etiologic factor in renal calculi.

The variation in the calcium and phosphorus metabolism in some of our cases observed over periods of months or years convinces us that the disease may have remissions and exacerbations. In such cases the gland apparently becomes overactive and then quiescent. The overactivity may never become very great, but this cycle continues over periods of years before the diagnosis is established. In such cases it may be very difficult to establish the diagnosis upon metabolic changes alone. An evaluation of the subjective and objective manifestations will aid in making the decision as to whether or not the parathyroid glands should be explored or the patient should be examined at frequent intervals in hopes of observing a period of overactivity of the gland.

As a rule the subjective and objective findings make the diagnosis without question. The bone pathology, increased serum calcium, de-

creased serum phosphorus, and elevated blood phosphatase establish the diagnosis fairly well, provided other destructive bone lesions are excluded. In cases with bone lesions without demonstrable alteration of calcium and phosphorus metabolism, exploration of the parathyroid glands may be necessary to establish the diagnosis. It should be borne in mind, however, that abnormal parathyroid tissue may be present and not discovered at operation; also, that the parathyroids may become hyperplastic secondarily to other disease and the discovery of this does not establish the diagnosis of primary hyperparathyroidism. In other cases evidences of bone pathology and renal calculi may be absent and the diagnosis is strongly suspected from the subjective manifestations and metabolic alterations.

SUMMARY

Thirteen cases of hyperparathyroidism are reported, all of whom lived in the middle-western part of the United States. The manifestations present and those which caused the disease to be suspected and, in addition, the diagnostic difficulties are discussed.

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Hexestrol: Clinical Study of a New Synthetic Estrogen

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THE DISCOVERY of the estrogenic properties of certain stilbene derivatives by Dodds and coworkers (1–3) in 1937, and the further demonstration of its estrogenic activity by others (4–5) led to the introduction of diethylstilbestrol into clinical use. To date a large number of clinical reports have demonstrated the therapeutic value of diethylstilbestrol, but the drug has the drawback that its administration is followed by nausea and vomiting in a variable percentage of cases.

Further search for the ideal synthetic estrogen that would not cause these toxic symptoms led to the study of a new compound isolated by Campbell and coworkers (6–7) which was identified by them chemically as 3,4-di-p-hydroxyphenyl-n-hexane and named hexestrol. These and other workers (8–11) have demonstrated the estrogenic properties of this new compound, hexestrol. Bishop and coworkers (11), Freed (12), and Bieren and Compton (13) have reported clinical studies on hexestrol. There is much discrepancy in these three reports concerning the relative activity of hexestrol, as compared with diethylstilbestrol, which demonstrates the need for further controlled studies of this new estrogen to determine its biological activity and to study its toxicity.

This report is concerned chiefly with the toxicity of the drug as shown by the amount of nausea and vomiting it produces, and by laboratory tests. Previous investigators have found that hexestrol is less toxic and less potent than diethylstilbestrol (13).

Permission to do this research was granted by the Research Committee of the Jefferson Davis Hospital, Houston, Texas.

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Hexestrol was furnished for this study in tablets of 0.2, 1 and 3 mg., in a solution in corn oil containing 1 mg. per cc. and in crystalline form, from which a solution in olive oil containing 25 mg. per cc. was prepared.

TABLE 1. INCIDENCE OF NAUSEA AND VOMITING WITH HEXESTROL BY MOUTH

Daily Dose	Patients Treated	Patient Exhibiting Nausea	Patients Exhibiting Vomiting
mg.	*no.*	*no.*	*no.*
1	18	0	0
2	22	0	0
3	12	0	0
6	15	0	0
9	18	4	0
12	26	5	0
18	19	5	0
24	21	6	1
Total	152	20	1

TABLE 2. INCIDENCE OF NAUSEA AND VOMITING WITH HEXESTROL PARENTERALLY

Injection 2-3/wk.	Patients Treated	Patients Exhibiting Nausea	Patients Exhibiting Vomiting
no.	*no.*	*no.*	*mg.*
50	20	4	1
75	23	16	6
100	19	14	12
125	12	11	11
200	13	13	12
250	10	10	10
300	8	8	8
500	5	5	5
1000	6	6	6
Total	116	87	71

It is apparent, from tables 1 and 2, that hexestrol produces nausea and vomiting less often than diethylstilbestrol. The total incidence of nausea following oral administration was 13 per cent. Patients could tolerate 50 mg.

of hexestrol intramuscularly without nausea, but when 75 to 100 mg. was given, approximately all (95%) of the patients had nausea, and when 125 mg. was given, all of the patients developed nausea within 4 to 6 hours. Fifty per cent vomited from 1 to 5 times the first day. On the second, third and fourth days there was nausea only; there was no nausea subsequently.

In contrast, 87 per cent of the 3223 patients receiving diethylstilbestrol experienced nausea after 5 mg. orally or after an injection of 5 mg. of the drug (14–16). From this data it can be concluded that if diethylstilbestrol and hexestrol are given in similar dosages, diethylstilbestrol causes an incidence of nausea over 6 times that of hexestrol.

To compare hexestrol with diethylstilbestrol, in regard to the production of uterine bleeding, 26 menopausal and 28 normally menstruating patients were given 3, 6 and 12 mg. of hexestrol orally 2, 3 or 4 times a day.

The reason for giving hexestrol in the above dosages was to learn if it was possible to produce uterine bleeding similar to that produced by 1 mg. of diethylstilbestrol daily for a period of 20 to 46 days (17). Regardless of the amount of hexestrol given none of the menopausal patients bled. This is an advantage over diethylstilbestrol since 52 menopausal patients had bled after taking diethylstilbestrol in 1 mg. doses daily for 20 to 46 days, even though they had not had a menstrual period for 1 to 28 years. In the earlier studies some of the patients who continued taking the 1 mg. doses of diethylstilbestrol after bleeding started, flooded so badly that they had to be hospitalized and have a dilatation and curettage in order to stop the bleeding (17). Later it was found that this bleeding could be more easily and conveniently controlled by giving from 10 to 25 mg. of diethylstilbestrol by mouth every 15 minutes until the bleeding stopped, which was within 4 to 6 hours (17).

Nausea. The percentage of 152 cases experiencing nausea as the result of 3 to 6 mg. of hexestrol daily was 12 per cent, while that resulting from 3 to 6 mg. of diethylstilbestrol daily was 87 per cent (18). The nausea from hexestrol in these doses was very mild and was not followed by vomiting in any instance. Therefore, it is our impression, from this study, that hexestrol is preferable to diethylstilbestrol for the treatment of menopausal symptoms.

It has been observed, as reported by Bieren and Compton (13), that some patients who were not relieved of menopausal symptoms with diethylstilbestrol were relieved when given hexestrol, and vice versa. There were also a few menopausal patients who were not relieved of menopausal symptoms by either of these synthetic estrogens, but who were relieved by taking natural estrogens. Patients who had received both diethylstilbestrol and hexestrol for menopausal symptoms preferred the latter because it did not produce nausea.

Normal menstrual cycle. Twenty-eight patients in whom menstruation was diagnosed as normal by means of a premenstrual biopsy, were given 3, 6, 9 and 12 mg. of hexestrol orally 3 times a day for 96 days. Endometrial biopsies were made premenstrually during the treatment and every second month after hexestrol; in every instance the biopsy tissue revealed normal premenstrual endometrium. From this it is apparent that hexestrol is much less potent as an estrogen than diethylstilbestrol, since 30 women with normal menstrual periods who took 0.5 mg. of diethylstilbestrol daily did not menstruate regularly and the endometrium was never premenstrual in character (17, 18).

The patients were required to keep accurate charts of the menstrual cycles every month. The 28 patients who received 18 to 27 mg. of hexestrol per day, reported that the menstrual flow was as regular as usual but that the amount of flow was less. Hexestrol given in these doses produced hypomenorrhea.

Dysfunctional uterine bleeding. Since the above observation indicates that hexestrol might be used in the treatment of dysfunctional uterine bleeding, 18 such cases were treated with hexestrol as follows: *a*) In cases in which bleeding had already stopped, 6 mg. was given 3 times a day for 6 months along with tolerated doses of thyroid. Accurate menstrual records showed in each case that bleeding recurred cyclically and was normal in amount and duration. *b*) If the patients were bleeding profusely, 100 to 250 mg. of hexestrol was given into the anterior wall of the cervix, or intramuscularly, using a spinal needle and a 10 cc. syringe. Following this, 3 to 6 mg. of hexestrol was given 3 times a

day. Bleeding usually stopped in from 2 to 8 hours after the large dose of the drug. All of the patients were nauseated and 82 per cent vomited at least once within 5 to 12 hours after the large dose of hexestrol was given. In all of the 18 cases menstruation became normal lasting from 1 to 3 days less than the usual time. The patients estimated that the amount of flow was reduced 25 to 50 per cent.

Dysmenorrhea. In 6 cases of dysmenorrhea 3 to 6 mg. of hexestrol was given 2 to 3 times a day. Five of the 6 reported that the flow was less in amount and duration and were relieved of dysmenorrhea. The sixth patient had more pain than usual at menstruation.

Senile vaginitis. Eight women having senile vaginitis were given 3 to 6 mg. of hexestrol, 2 to 3 times a day. The thin atrophic vaginal mucosa came to resemble that of the normal vagina. Two of the 8 patients became nauseated and stopped the drug. The pH of the vagina, as determined by a Beckman pH instrument, was 7.23 before the hexestrol was given and after 5 to 6 days the pH was 4.8 to 5.2. When hexestrol or diethylstilbestrol is given (0.5 mg. or more per day over a period of 20 days or longer), a marked hyperplasia of the cervical glands is produced with the result that cervical secretion with a pH of 7.6 to 8.0, passes out of the cervix and a false reading of the vaginal acidity will result if this possibility is not taken into consideration.

Gonococcal vulvovaginitis. Three patients with a gonococcal vulvovaginitis were given 1 to 3 mg. of hexestrol by mouth daily for 14 to 28 days. The vaginal smears became negative within 7 to 9 days. A fourth case has been hospitalized for 32 days and takes 3 mg. of hexestrol daily. The smears continue to be positive for gram-negative intracellular diplococci.

Laboratory Studies for Toxicity

The toxicity of hexestrol has been studied by doing routinely, before the beginning of therapy and every 2 to 6 weeks thereafter, complete blood counts, urine analysis, blood cholesterol, blood Ca, uric acid, blood sugar, NPN, electrocardiograph and blood Cl determinations, and roentgenograms of the sella turcica. No abnormal changes in the blood were found that would indicate toxicity. In one series of 143 women there were 597 blood studies made.

Thirty-two patients who were scheduled for some type of gynecological operation were studied and were given, prior to operation, a total of from 14,000 to 15,000 mg. of hexestrol in from 1 to 214 days as shown in table 3.

TABLE 3. DOSAGES OF HEXESTROL USED IN TOXICITY STUDY

Case	Total Dosage	Days of Treatment
	mg.	
1	2,692	102
2	3,368	47
3	3,479	92
4	648	28
5	2,343	102
6	4,455	180
7	2,878	44
8	300	3
9	500	3
10	315	1
11	1,211	82
12	1,542	43
13	776	126
14	800	101
15	2,565	103
16	612	88
17	2,188	110
18	1,230	185
19	1,602	140
20	2,064	157
21	15,000	214
22	5,630	86
23	4,125	92
24	1,980	92
25	1,002	49
26	109	54
27	4,250	89
28	1,167	102
29	111	112
30	315	93
31	250	1
32	14	14

This study made it possible to determine at the time of operation the effect of these amounts of hexestrol upon the female generative organs and to examine in many of the patients sections of the myometrium, cervix, vagina, endometrium, tubes and ovaries. There was no evidence of malignant changes and no abnormal pathology produced. The menstrual history was carefully recorded on these patients before, during and after the administration of the hexestrol.

In this group of 32 patients there were no abnormalities in the laboratory tests or in roentgenograms of the sella turcica before, during and after giving hexestrol. This would seem to indicate that hexestrol is a relatively non-toxic drug.

Fifteen patients were made amenorrheic for

periods ranging from 2 to 6 months by taking from 50 to 500 mg. of hexestrol daily. Their respective normal menstrual cycles were resumed after hexestrol was discontinued, and have remained normal for 6 to 18 months.

Patients who were nauseated by hexestrol did not develop a tolerance for it upon continued administration as is the case with diethylstilbestrol (18). Pregnant women were more sensitive to hexestrol than to diethylstilbestrol since 100 mg. of hexestrol given 3 times a week over a period of 2 to 16 weeks will more often nauseate the pregnant patient than the non-pregnant woman receiving the same dosage for the same period of time. As a rule, both pregnant and non-pregnant patients will become tolerant to diethylstilbestrol within 4 to 5 days (14, 15, 16, 19–24). There are exceptions to this, of course.

SUMMARY

Hexestrol which is a relatively weak estrogenic drug has been found useful in therapy of the menopause, dysfunctional uterine bleeding, juvenile vulvovaginitis and senile vaginitis.

In cases of menopause hexestrol was more effective than diethylstilbestrol because there was less nausea and no uterine bleeding as with diethylstilbestrol.

Doses of 3 mg. 1 to 3 times a day, were effective for the treatment of dysfunctional uterine bleeding and menorrhagia. The 3-mg. tablets were given at 9 P.M. for 3 nights, then one 3-mg. tablet 3 times a day for 3 days. The 3-mg. dose was gradually increased every day until tolerance was reached, which was usually 3 to 6 mg., three times a day. The medication could be taken only at night if the patient wished. If the bleeding was severe, 75 to 100 mg. of hexestrol was injected at once into the anterior wall of the cervix or intramuscularly, followed by 6 to 9 mg. orally every 15 minutes until bleeding stopped, then 6 to 9 mg. 3 times a day for 3 to 4 months along with 1 to 5 grains of thyroid per day for 6 to 12 months. In the case of nausea, nembutal, 1½ grains or phenobarbital was given.

In menopause cases, the patient was given 0.5 mg. of hexestrol orally 3 times a day for 2 days, then the dosage was increased by 0.5 mg. every 2 days until the patient determined the amount required to relieve the menopausal symptoms.

Due to the fact that we were unable to produce uterine bleeding with hexestrol, as occurs with diethylstilbestrol, and that we could control 89 per cent of the menopause cases with hexestrol, we believe hexestrol should be used instead of diethylstilbestrol for the treatment of menopause symptoms.

Laboratory tests before, during and after the administration of hexestrol were normal, so it is apparent the drug is not very toxic even in large unphysiological and experimental doses.

I wish to thank the following for the generous help given in this research; the laboratory technicians, residents, interns, and nurses at the Jefferson Davis Hospital, the physicians of Houston, Texas, who have given reports of their results with hexestrol; Miss J. Miller Hutcheson and Miss Jane Klabechek, research technicians, Miss Gladys Racker and Miss Doris Dillehay, research nurses and Dr. Peter Marcuse and Dr. W. W. Coulter, pathologists.

The hexestrol was generously supplied through the Wm. S. Merrell Company, Cincinnati, Ohio. The thyroid used was supplied by the Armour Laboratories, Chicago, Illinois.

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Estrogen Pellet Therapy in the Menopause

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IN THE TREATMENT of patients with menopausal symptoms, estrogen replacement therapy has earned for itself a well-established place. The procedure of administering the hormone parenterally two or three times a week, in order to maintain a sufficient level in the tissues, has decided disadvantages; it is time-consuming for both the patient and the physician, and the frequent hypodermic injections are disagreeable. In order to circumvent the inconvenience and unpleasantness of administration, the use of the orally active estrogen, stilbestrol, has become widespread among gynecologists and practitioners.

There can be no doubt of the effectiveness of stilbestrol in controlling menopausal symptoms, but its administration is often associated with undesirable side effects. We have found that 12.5 per cent of 32 patients in the dispensary, and a much higher percentage among private patients, who were treated with oral stilbestrol, were required to discontinue it because of nausea and vomiting. It has been demonstrated that many patients can take very small doses of stilbestrol without nausea or vomiting, but the percentage of relief of symptoms in a dosage of 0.5 mg. or less is much smaller than when the dosage is increased to 1.0 mg. daily. When this dosage, 1.0 mg. daily, is used, nausea and vomiting often necessitate discontinuance of the therapy.

Uterine bleeding is another side effect which is frequently noted when stilbestrol is given orally. When stilbestrol was administered in daily dosage of 0.5 mg. or less, there was uterine bleeding in 8.8 per cent of the cases; of the group which had received a dosage of 1 mg. or more per day, 36.3 per cent bled abnormally. Since a dosage of 1 mg. or more is frequently necessary for relief of symptoms, it is obvious that bleeding in over a third of the cases is a decided disadvantage. In a small group of 7 cases we attempted pellet implantation with stilbestrol. Five of the 7 women bled abnormally, an incidence too great to make implantation with stilbestrol a practical method of treatment. It is noteworthy, however, that all of these 7 women were relieved of their menopausal symptoms. The bleeding is usually not profuse but occurring, as it does, during years when malignancy must always be seriously considered, a curettage is necessary to rule out cancer. The disadvantage of bleeding, of course, does not apply to those cases of the surgical menopause in which there is no uterus; it is in this group that we believe stilbestrol to be most useful.

Because we have not been entirely satisfied with either the parenteral use of the natural estrogens or with the oral use of stilbestrol, we have sought another method of administering the hormone. In 1937, Deanesly and Parkes (1) announced a new technique in hormone administration in animals whereby solid pellets of crystalline hormone were implanted subcutaneously, to be absorbed slowly and continuously over a long period of time. Such pellets were found effective in producing prolonged hormonal stimulation in laboratory animals. In 1938, Bishop (2) implanted a pellet of estrone subcutaneously in a young castrated woman who reported partial relief of menopausal symptoms; this relief lasted for 5 weeks. In 1940, Bennett, Biskind and Mark (3) reported their results on 21 menopausal women treated with subcutaneous pellets of theelin

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(estrone). They found that relief of subjective symptoms began on an average of 2 weeks after the implantation and persisted for as long as 14.5 weeks. They also discovered *a*) that the urinary estrogen level rose and remained elevated for correspondingly long periods, *b*) that the urinary level of gonadotropic hormone was depressed in 60 to 70 per cent of the cases and *c*) that prolonged stimulation of the vaginal mucosa occurred as observed in biopsy specimens. These objective findings were interpreted as showing, beyond doubt, that the theelin was absorbed continuously from the pellets over long periods, and that the estrogenic action of the absorbed theelin was not impaired by the pellet method of administration.

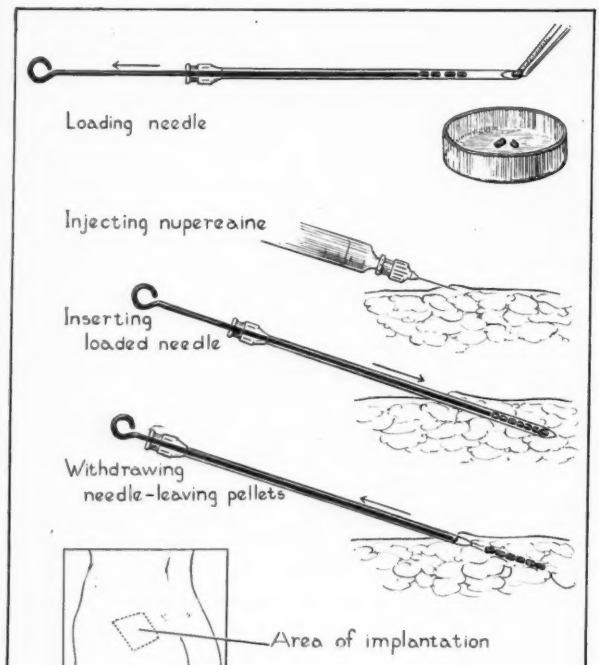

FIG. 1.

In a previous publication (4) we have reviewed the work of MacBryde, Freedman, Loeffel and Allen (5) on the implantation of pellets of stilbestrol through small incisions and we have also reviewed the work done by Twombly and Millen (6) with 20 mg. pellets of estradiol implanted through a 10-gauge needle. In the same publication we cited the work of Mishell (7) who implanted large pellets of crystalline estrogens obtained by extracting pregnant mare's urine. One pellet was implanted in each instance through a small incision just above Poupart's ligament. Eighteen of 19 women so treated were relieved of their menopausal symptoms. We reported in a previous publication (4) our results in 45 women treated by implanting multiple small pellets of theelin (estrone), and described the technique which we employed. Since then we have had a much larger experience based upon a total of 225 implantations in 133 patients and it is upon this experience that we wish to report. Because the technique of implantation is not yet generally known we will describe it here.

TECHNIQUE

The pellets are made by direct compression of crystalline estrone by means of a punch and hammer in a steel plate, bored with small cylindrical openings 1.8 mm. in diameter. A solid steel plate is screwed tightly beneath this plate to hold the material in the small cylindrical compartments. After the pellets have been compressed the lower solid plate is removed and the pellets punched out. They are 1.83 mm. in diameter and vary from 2 to 5 mm. in length and weigh from 5 to 10 mg. each. Such pellets could be made easily on a commercial basis, but they are not yet available. Labor and material shortage due to the war has prevented their manufacture. The pellets are sterilized in a dry steam autoclave at 250° F. under 15 pounds of pressure for 30 minutes. The implantations are made through a 12-gauge hollow needle fitted with a stilet (fig. 1). The pellets are loaded, with a sterile forceps, into the pointed end of the needle, after the stilet has been withdrawn.

The skin over the gluteal region is prepared

by painting with full strength tincture of iodine which is allowed to dry and then washed off with alcohol. A spot is infiltrated with 1:500 nupercaine solution and the loaded needle inserted obliquely beneath the skin. As the needle is withdrawn the stilet is pressed in and the pellets are implanted subcutaneously. A small dry gauze dressing is placed over the injection site and left there for a week. The implantation is quite painless and can be done easily as an office procedure.

Because a foreign object is being introduced into the tissues, the most rigid sterile technique must be observed. In over 225 implantations we have had 3 relatively severe infections, and these occurred in the earlier days of our experimenting when the skin was prepared with alcohol alone. In none of these cases of infection did the implanted pellets slough out but there was a rather indurated, reddened area at the site of implantation. This necessitated the use of a protective dressing for a few weeks; in one instance, hot applications were used.

It is interesting to note that these cases complicated by local infection showed little or no relief of symptoms. This indicated, we believe, poor absorption due to fibrosis and to diminished blood supply about the infected foreign material. One of the patients, who had a local infection and who received no relief, had had a previous implantation with complete relief. A third implantation which was free from infection, resulted, again, in complete relief.

Because, then, of this danger of infection, the gluteal region is prepared for implantation by painting with full strength tincture of iodine and washing it off with alcohol. Since we have used this method of antisepsis we have had no infections and conclude that the danger of infection is negligible when proper technique is followed.

Dosage. In our last 150 implantations we have standardized the dosage at 50 mg. This amount of hormone usually is contained in 6 to 7 pellets. Smaller dosage would shorten the period of effectiveness, and greater dosage, representing a larger quantity of foreign material, would enhance the foreign body reaction about the pellets and, possibly, increase the danger of infection.

CLINICAL RESULTS

In evaluating results we have, as have most other investigators, considered the relief of hot flashes to be the most definite criterion of success. In our first publication (4) we reported satisfactory results in 93.4 per cent of the treated cases. In our present larger series of 133 patients in whom 225 implantations were made, the results have continued to be equally good. Approximately two weeks usually pass before sufficient estrone is absorbed to become effective. There are exceptions to this rule, however, for we have observed a complete cessation of menopausal symptoms within a week after the implantation. On the other hand, in a few individuals, a month has elapsed before the flashes have subsided. If no benefit is observed within a month there is usually no subsequent benefit. As a rule the flashes disappear gradually, there being a progressive diminution in intensity and frequency. With the subsidence of the flashes the feeling of nervous tension likewise disappears, and a feeling of well-being is established.

The relief of symptoms lasts, on an average, 4 months, but occasionally the flashes return after a shorter lapse of time; relief for 7 to 8 months is not uncommon. In a few instances, there has been no return of menopausal symptoms for an observed period of two years. We are inclined to regard these permanent 'cures' as cases in which the menopausal symptoms would have been of relatively short duration even without the implantations. We have seen no evidence that the normal period of adjustment of menopause is shortened by this substitutional therapy; nor have we been able to observe that it is lengthened. When the flashes do recur after a period of freedom, following an implantation, they usually recur in a milder form and are easily controlled by another implantation. Six is the maximum number of implantations which we have given to any one patient. These implantations have been given during the last 3 years, and at each implantation relief has been afforded.

It has become apparent to us that the best

results are seen in women who are treated relatively early after the onset of symptoms. The results are not as striking in those cases in which menopausal symptoms have been present for 3 or 4 years, the patient having become entrenched in her symptomatology. Also, one cannot be certain of the success of implantation treatment in obviously neurotic women; it is difficult, in dealing with them, to separate the real from the purely neurotic symptoms. However, we have used it, at times, as a therapeutic test in such individuals, and have frequently been surprised in the marked improvement in some of the patients whose symptoms we were inclined at first to regard as neurotic rather than menopausal.

With the exception of a few cases of infection at the site of implantation, which we have noted above, we have observed no untoward effects. Abnormal bleeding occurred only once in our first 28 cases previously reported, and we have seen it only a few times in the larger series of 133 cases. Since abnormal bleeding is common during the menopausal years one might expect coincidental bleeding occasionally. In fact, in a series of control patients which were treated with luminal, there was abnormal bleeding in 6.3 per cent, a greater incidence than occurred in our patients treated with estrone implantations.

CONCLUSIONS

From an experience of 3 years with the implantation of estrone (theelin) pellets we have concluded that it is the most satisfactory method yet proposed of treating the menopause. It has the advantage over the parenteral administration of the estrogenic hormone in oil in that one implantation results in a sustained absorption and prolonged relief of symptoms. It has the advantage over the oral administration of stilbestrol in that there are no untoward gastrointestinal symptoms, and there is no evidence that uterine bleeding is induced by it as is frequently the case with stilbestrol. The method is safe when proper methods of antisepsis are used, and it is sufficiently simple to carry out as an office procedure.

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A Case of Myxedema with Macrocytic Anemia Successfully Treated with Thyroid and Testosterone

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THAT myxedema is usually associated with anemia is a well established clinical observation. It has also been observed that thyroidectomy in the experimental animal or in man is followed in the majority of cases by a moderate anemia. Stern and Altschule (1) reported that hyperchromic and macrocytic anemia of moderate severity complicated total thyroidectomy in a group with heart disease. The latter anemia resembles exactly the simple hyperchromic type described by Bomford (2), in his classification of the anemias in spontaneous myxedema, as the uncomplicated anemia of myxedema. He regards it as a result of a decrease in the size of the erythron which takes place in hypothyroidism as a physiologic compensation for diminished need of the tissues for oxygen, and to be akin to the anemia which appears in animals exposed to atmospheres of oxygen tension greater than normal. In other words, Bomford considers that thyroxine influences erythropoiesis only indirectly, insofar as the consumption of oxygen by all tissues is concerned, or as it may affect gastric secretion. He further observes that

> this simple hyperchromic anemia is never severe, the color index is normal or a little above one. There is some macrocytosis but no poikilocytosis and no excessive anisocytosis. The reticulocyte count may be normal or a little above normal. The gastric function may be normal or there may be achlorhydria. The administration of liver or of iron has no effect on the anemia but the anemia does respond slowly to treatment with thyroid alone, in such doses as are found to keep the patient free from symptoms of myxedema or overdosage. The rate of response is very slow, the blood count attaining normal levels in from three and a quarter to nine months.

In the light of more recent clinical and experimental observations it seems that this process of the regeneration of the blood may be enhanced or augmented by the addition of testosterone to therapy with thyroid extract. In the treatment of hypogonadal males in recent years it is not uncommon to note a striking increase in the blood count after the administration of testosterone. The hypochromic anemia of the eunuchoid responds readily to treatment with androgens. Experimental observations such as those of Steinglass (3) indicate that testosterone stimulates, whereas estrogen depresses, the function of the bone marrow.

McCullagh and Jones (4) also demonstrated that testosterone raised the blood count of hypogonadal males and that withdrawal of the hormone lowered both the hemoglobin and the count of the erythrocytes.

Because of the above observations the case being reported herewith was subjected to a trial of combined thyroid and testosterone therapy.

CASE REPORT

On Aug. 8, 1938 a 71-year-old male, E. W. W., was admitted to the hospital with the diagnosis of a refractory pernicious anemia complicated by cardiac decompensation. He had been treated for many months prior to admission with liver extract and iron, without benefit. In the hospital the myxedema and cardiac failure were quite apparent, as was the anemia. The history indicated progressive intolerance of cold, weakness, somnolence, unsteady gait, pronounced bloating (especially unusual puffiness of the eyes), dry

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skin with sparse lifeless hair on the scalp and body, thickness of the tongue, croaking voice and very dull mentality. The symptoms had been coming on for 3 to 5 years, the exact onset being uncertain.

Physical examination revealed a classical example of spontaneous myxedema (fig. 1, left). The skin was edematous, of cafe-au-lait color; the voice hoarse and croaking; the tongue smooth and thick. There was no lymphadenopathy; the right submaxillary salivary gland was hard and about 3×2 cm. in size. The thyroid was slightly larger than normal. The heart was very much enlarged, its tones distant, the rate 62 and the rhythm regular; the blood pressure was 160/105 mm. Hg. There was passive congestion of the legs, liver and lungs; the presence of ascites was uncertain. All psychosomatic reactions were sluggish. The initial laboratory findings are depicted in table 1.

The initial electrocardiogram showed the characteristic depression of the T wave as well as a widened QRS complex (fig. 2, left), which is less constant in myxedema. The chest roentgenogram revealed marked enlargement of the heart and some pulmonary passive congestion (fig. 3, left).

FIG. 1 (*left*). *Patient E.W.W.* when first hospitalized for treatment of myxedema heart and macrocytic anemia. August, 1938. (*right*). Patient after thyroid administration had relieved the cardiac decompensation. Note loss of myxedema. October, 1938.

TABLE 1. RESULTS OF MISCELLANEOUS DIAGNOSTIC TESTS ON ADMISSION, AUGUST 8, 1938

B.M.R., %	minus 50
Blood cholesterol, mg.	278
Icteric index, units	11
Total blood protein, gm.	7
Gastric analysis	Free HCl 65°
Venous pressure, cm. Hg	15
Venous pressure after r.u.q. pressure rise to	22.5 cm.
Circulatory time: arm to lung, seconds	13
arm to tongue, seconds	31
Blood volume index	1.1
Sternal puncture, marrow	normoblastic

BLOOD COUNT

Hb. (Sahli)	61%	*Smear:*	
r.b.c.	2,800,000/cu. mm.	macrocytes	++
c.i.	1.1	slight anisocytosis	
w.b.c.	3.000/cu. mm.	occasional polychromatophilia	
neutrophiles	52.0%	occasional stippled cell	
eosinophiles	4.0%	platelets, normal number	
lymphocytes	38.0%		
Reticulocytes	1.6%		

With continued thyroid feeding there was complete clearance of myxedema and a gradual return of a sense of well being. But there was no improvement in the anemia during the entire hospital regimen of almost 3 months. The blood count remained practically unchanged. One brisk reticulocytosis was followed by a fairly stable normal reticulocyte count. Figure 4 indicates the blood count in percentage of the normal, assuming 5,000.000 r.b.c./cu. mm. as normal; and the B.M.R., which returned to normal levels before discharge from the hospital. It is self evident that the

It may be safe to assume that this cardiopathy was the result of myxedema, but a moderate hypertension may also have been contributory. In keeping with this diagnostic evaluation was the prompt and satisfactory response of the heart failure to bed rest and thyroid extract alone. Digitalis was not necessary. The striking shrinkage in the size of the heart as well as the progressive increase in the positive character of the T wave became apparent after thyroid therapy (fig. 3, right).

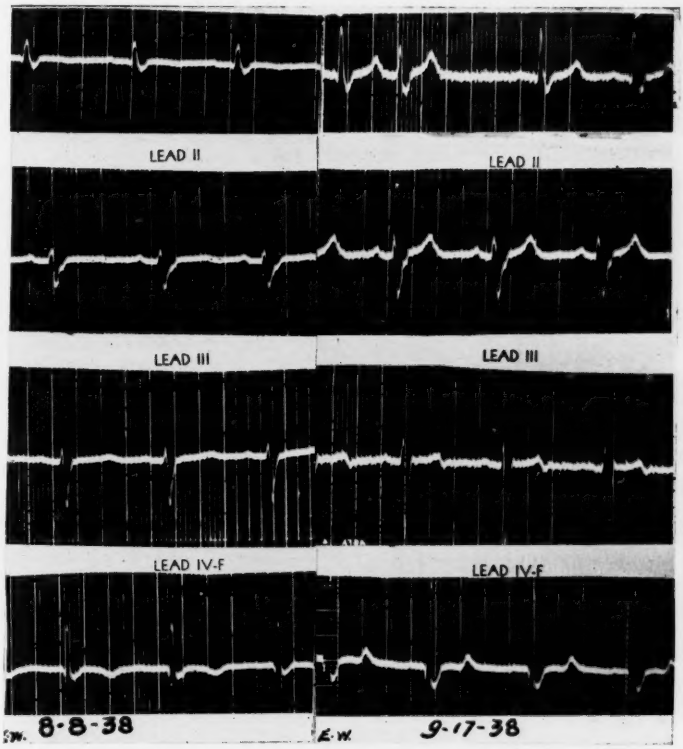

FIG. 2. Myxedema heart *a*) on admission showing the characteristic depression of the T wave and the less typical widening of the QRS complex; *b*) after 5 weeks of bed rest, showing positive T wave; widening QRS complex still present.

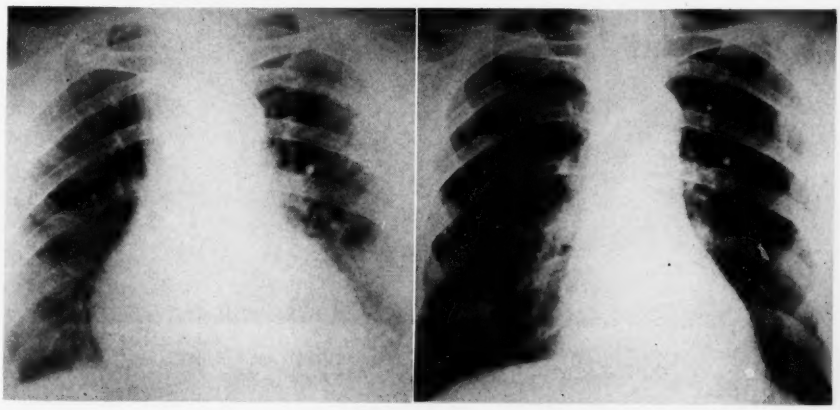

FIG. (3 *left*). Myxedema heart with congestive failure. Aug. 10, 1938. (*right*) Striking shrinkage in size of heart after bed rest and 2 grains of thyroid daily. Sept. 19, 1943.

cure of the myxedema was accompanied by a considerable loss of weight (fig. 1, right).

Liver extract and iron was tried for a short period but without any apparent effect on the blood count. seemingly failed to influence erythropoiesis, testosterone propionate was injected intramuscularly in 10-mg. doses twice weekly. Methyl testosterone was substituted after 450 mg. of testosterone propionate

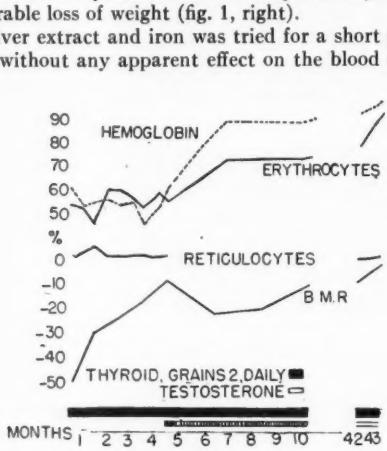

FIG. 4. Response of blood count in percentage of normal in a case of spontaneous myxedema, after treatment with thyroid and testosterone. The control period of 4 months, during which treatment with iron, thyroid and liver extracts was followed by treatment with *a*) testosterone propionate, 450 mg. within a period of 2 years, and *b*) methyl testosterone, 1000 mg. within following 1 year; 200 mg. of the methyl testosterone was given within the first 10 days of the last month shown to induce a brisk rise in the blood count. A slight rise in the B.M.R. but no change in the reticulocyte count was noted. A prompt erythropoietic response to testosterone is apparent at the beginning and end of the period of observation. The initial rise in blood count was sustained throughout. Note break in the curve to indicate lapse of 30 months during which there were no significant changes in any of the factors depicted.

It is noteworthy that thyroid extract given in dosage greater than 2 grains daily was apt to induce angina—hence this nominal dose has been maintained to date had been given. To date about 1000 mg. of the methyl testosterone has been administered orally along with the daily maintenance dose of 2 grains of thyroid.

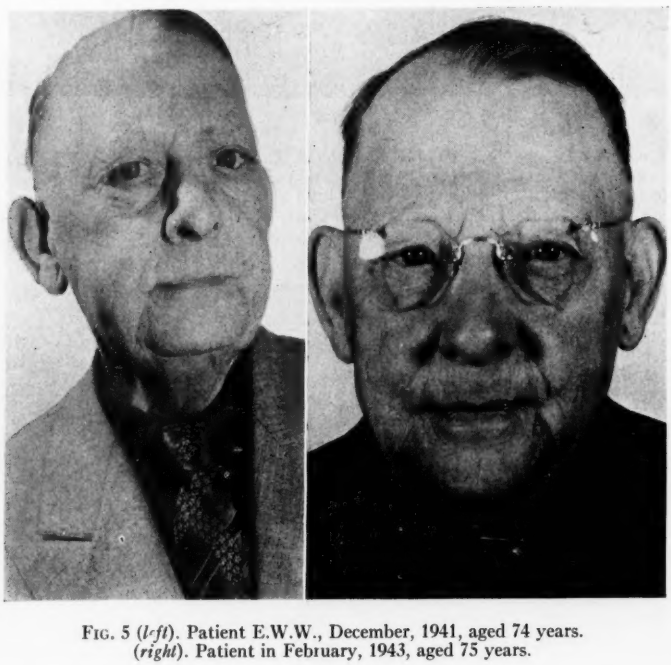

FIG. 5 (*left*). Patient E.W.W., December, 1941, aged 74 years.
(*right*). Patient in February, 1943, aged 75 years.

(with occasional intermittance of one week's duration), with satisfactory symptomatic control.

In order to hasten the cure of the anemia it was deemed advisable to test the effect of testosterone. In January, 1939, after 4 months of thyroid feeding had The dosage of testosterone has been kept minimal (1500 mg. in 3 years) as a precautionary measure, because, with the marked improvement in the patient's well being, it became increasingly difficult to restrain his physical activity. With a questionable

myocardium in a senescent male it is better to err on the side of an insufficiency rather than too much testosterone.

The response of the blood count to this combined therapy was prompt and very gratifying. It can be seen in figure 4 that even less than a physiologic dose of testosterone stimulated a prompt and substantial rise in the hemoglobin and the erythrocytes. This was sustained at slightly subnormal levels until a more physiologic dose of methyl testosterone (200 mg. in

TABLE 2. BLOOD STUDIES, FEBRUARY 8, 1943

Hb.	91% (Sahli)	neutrophiles	49.5%
r.b.c.	4,790.000/cu. mm.	eosinophiles	5.5%
w.b.c.	8.000/cu. mm.	basophiles	1.5%
		lymphocytes	32.0%
		monocytes	11.5%
	Smear, normal		

Hematocrit	44 Vol. %
Reticulocytes	1.7 %
Blood vol. index	0.88 %
Color index	0.9

10 days) was administered this year. This restored the blood count to normal. Note that the B.M.R. and body weight were likewise stimulated to a more normal status by this increased dose of testosterone.

The character of the recent blood smear is in sharp contrast to that of those before treatment with thyroid. The macrocytes disappeared fairly early, the erythrocytes assuming normal shape, size and color during therapy (table 1 and 2). Figure 5 shows a gratifying transition of the patient from classical myxedema to normality.

DISCUSSION

Recent clinical (4) and experimental work supports the concept that the endocrines influence erythropoiesis. This is particularly true of the thyroid and testicular hormones.

It might be speculated that inasmuch as the cure of the above discussed anemia was facilitated by the addition of testosterone to the usual thyroid therapy, any elderly or hypogonadal male with myxedema associated with anemia should profit by similar treatment. Here one may anticipate an augmentation of the anemia by the hypogonadism. If this were true, then thyroid and testosterone would provide a more logical type of therapy than either one alone. Moreover, the patient is more promptly and completely rehabilitated with such combined therapy. To restore promptly a sense of normal well being by judicious combined organotherapy seems very worth while in such patients since time is of the essence in these situations.

In this connection one may further speculate on the value of combined thyroid and androgen treatment of certain refractory anemias, especially the so-called achrestic anemias, and those without apparent etiology other than senescence. The positive stimulation of the bone marrow by these hormones may provide a missing therapeutic link. Inasmuch as many of such anemias terminate fatally, judicious experimental trials with this organotherapy may be regarded as harmless.

SUMMARY

An elderly male with a chronic untreated myxedema presented an associated hyperchromic macrocytic anemia. Four months of treatment with thyroid, liver extract and iron was without apparent influence on the anemia. When testosterone was added to the thyroid therapy the erythropoietic response was prompt and complete. It is suggested that similar anemias be given trials of such combined organotherapy.

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EDITORIAL

THE ENDOCINE PUZZLE OF HETEROSEXUAL HYPERTRICHOSIS (HIRSUTISM)

AN EMBARRASSING mustache and beard with excessive hair growth elsewhere on torso and extremities occurs far more frequently in adult girls and women than is generally supposed. It constitutes a distressing affliction, oftimes a depressing torment and heartache for life.

Understandably, relief is sought at the hands of beauty specialists, before or after, or perhaps without ever consulting a physician. Often, sooner or later, in desperation, the patient is referred to an endocrinologist—for a miraculous 'gland-cure.' Hardly a month passes without the writer's being confronted with the unhappy duty of discouraging the victim's hopes and expectations.

For the majority of these unfortunates we have little to offer, either in explanation or therapy. Often the strange paradox has been uttered that it would be better for them if they were much worse—in that a cure might be possible if, in addition to superfluous hair of masculine distribution, there were also atrophy of the breasts, cessation of menses, and hypertrophy of the clitoris —pointing to an adrenal cortical tumor or an arrhenoblastoma of an ovary, removal of which could be counted upon to demasculinize and refeminize.

Extirpation of these androgenic-like tumors produces fairly prompt restoration of menstruation and gradual falling out of the abnormally-situated hair. The transformation would seem almost magical were it not convincing proof of the eradication of the underlying cause.

Unfortunately the overwhelming majority of hirsute women have no other complaints, and display no other abnormalities, than the heterosexual hypertrichosis. And in many of them it would appear to be simply an intensified familial racial characteristic, as in females of the Mediterranean peoples. A noticeable mustache at least is fairly common amongst them. It is more disconcerting and not readily explained when the hairiness exists in a female of English, Scotch or Scandinavian origin.

Not infrequently obesity accompanies the hirsutism. The fat may be confined to the upper half of the body ('buffalo' obesity, as in Cushing's disease), or restricted chiefly to the hips, buttocks and abdomen ('girdle' type), or fairly generalized. Measures undertaken to reduce the adiposity fails to influence the hypertrichosis.

In other cases menstrual intervals may be prolonged and the flow reduced, but this additional factor offers little if any help in devising methods to counteract the hirsutism.

Since it became known that both sexes secrete both male and female sex hormones, it was tempting to assume that in hirsute women the normal ratio between these hormones had been altered in the direction of diminished estrogen and augmented androgen production. Consequently it would appear plausible to attempt counteracting the androgenic trichosis by administering estrogens (stilbestrol, estradiol). The results of such attempts have not been encouraging.

Recently Albright, *et al.*,[1] in an article entitled "A Syndrome characterized by primary ovarian insufficiency and decreased stature . . . with a digression on hormonal control of axillary and pubic hair," suggests that, in females, this sexual hair is stimulated to grow by a hormone from the adrenal cortex. They claim further that pituitary dwarfs, whose adrenal cortices are atrophied secondarily, have no axillary or pubic hair, whereas females suffering from primary ovarian insufficiency usually have moderate amounts or can be stimulated to grow axillary and pubic hair by estrin therapy. However seductive such an hypothesis may be, the writer thinks it pertinent to note that he has had a 19-year-old girl under intensive estrin therapy for several months; she had never menstruated, had absolutely no mammary development, and was totally devoid of sexual hair; she was of stocky build but her height was within the limits of normal ($60\frac{3}{4}$ inches); most certainly she was not a pituitary dwarf. Estrin therapy has been successful in inducing vaginal bleedings and excellent mammary development, but not a single pubic or axillary hair has appeared during months of treatment.

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[1] ALBRIGHT F., P. H. SMITH AND R. FRASER: *Am. J. Med. Sc.* 204: 628. 1942.

It is not surprising that an adrenal cortical hyperplasia should be suspected as responsible for excessive hairiness in females (even in little girls), in view of the striking hirsutism and virilism, associated with adrenal cortical tumors and their cure by removal of the tumor. But bilateral partial adrenalectomy, for a supposed hyperplasia, is far too radical and hazardous a procedure for mere hypertrichosis, and inhibitory adrenal irradiation has not diminished the unpleasant hairiness.

In the absence of such an adrenal tumor or an arrhenoblastoma, endocrine therapy so far offers no solution for embarrassing beard and mustache, hair on the chest and thighs, and a masculine pubic escutcheon. Bleaching of the hair, in brunnettes, to render it less conspicuous, and skilful depilatory measures, are all that can be justifiably recommended. Electrolysis is an unending business and apt to be scarring if the beard is at all luxuriant.

H. L.

LETTER TO THE EDITOR

REVERSIBLE TESTOSTERONE-INDUCED VIRILISM

TO THE EDITOR:

The widespread use of testosterone propionate in the treatment of females with sexual and functional endocrine disorders has caused justifiable concern as to the dangers of induced masculinizing effects. Several reports in the literature have described virilism in the female as an unfortunate consequence of intensive androgenic therapy for gynecologic conditions such as dysmenorrhea, functional uterine bleeding and mastopathies. A case showing the transient nature of such masculinizing changes seems, therefore, worthy of mention since women who have become distressed over these changes may have some assurance that not in all cases are the change in voice, hairgrowth on the face, arms, legs and trunk, and enlargement of the clitoris, permanent disfigurements. Greenhill and Freed[1] have described the cases of two young women who received brief intensive courses of testosterone therapy and who developed alarming degrees of virilism.

Huffman[2] in a study of the effect of testosterone propionate upon reproduction in experimental animals (female rats) found that estrus was suppressed during androgen administration and that all female animals developed clitoridal hypertrophy. He points out that the androgenic effect of the male sex hormone on the female animals is secondary to pituitary changes and that this effect is maintained only a short time after the injections are discontinued. All of his experimental animals had a return of normal estrus and bore healthy litters within 68 days after the treatment was terminated. Their progeny also bore normal offspring. Mazer and Mazer[3] have reported that of 38 women under androgenic therapy, 4 subsequently experienced normal pregnancies.

The reversibility of virilism induced by administration of male sex hormone appears to be an entirely reasonable possibility since even in the most prolonged and pronounced cases of adrenal cortical virilism the acne, hirsutism, amenorrhea, gruff voice, breast aplasia, hypertrophy of the clitoris and other changes undergo gradual correction after removal of the adenoma as was shown in the case reported by Lukens and Palmer[4] in 1940.

Case report. The patient is a married woman of 27, the mother of a normal boy age 5. Before androgenic treatment was given she had suffered from pulmonary tuberculosis and after thoracoplasty the disease was arrested. She had experienced severe migraine at increasingly short intervals since the age of 15. The convalescence from tuberculosis was retarded because of the frequent bouts of nausea and vomiting brought on by the migraine and in consequence she was greatly underweight. Because of the general tonic and the weight-increasing effects of male sex hormone she was given daily intramuscular doses of 25 mg. of testosterone propionate in sesame oil over a period of 17 days (Oct. 28 to Nov. 14, 1942) and then 9 doses over a period of the next 18 days (Nov. 14 to Dec. 2, 1942). In 35 days she therefore received a total of 650 mg. of testosterone propionate. After 3 weeks she had experienced an improvement in appetite and had gained 10 pounds in weight. A rather severe acne appeared on the chest and on the back. At the end of the treatment the patient complained of a marked growth of long, dark hair on her upper lip, cheeks and chin, on her upper and lower extremities and abdomen. Three weeks after termination of the treatment the growth of hair was more marked, especially on the thighs and abdomen. Her voice had become husky, there was complete amenorrhea and the breasts had shrunk considerably. There was moderate enlargement of the clitoris. She was alarmed about these changes. There was no relief from the migraine headaches but she had gained a total of 15 pounds in weight. The hirsutism remained stationary from Dec. 23, 1942 until about the middle of February, 1943 (approximately 9 weeks) when the patient noted an absence of hair on the abdomen, absence of acne, and a marked diminution of the hair on the thighs. By March first the excess hair on the upper lip, chin and cheeks had disappeared, the enlargement of the clitoris had disappeared, the breasts had been restored to their normal volume and consistency, and the voice had returned to normal pitch and timbre. The menstrual cycle was re-established in January of 1943, 43 days after termination of androgen therapy, and the subsequent periods have been more normal than in the two years preceding the treatment. On March 20, 1943, 109 days after the last dose of testosterone, a review of the situation showed that all of the induced changes had disappeared, except that about half of the weight gain was retained.

Male sex hormone has many valuable uses in the treatment of gynecological and functional endocrine disorders in the female. Medical men must be cognizant of the fact that with intensive treatment disturbing masculinizing effects may be the untoward concomitants of successful symptomatic relief. While justifiably alarming it is worth noting that in the instance described above, in which the changes toward virilism were substantial, they were, however, reversible in character. As has been stated by numerous investigators the gain in weight is due in part to the increased water retention but it is also attributable to the improved feeling of well-being and enhancement of appetite and general metabolism.

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Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: DANIEL A. McGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. DONALDSON, J. W. EVERETT, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, HANS O. HATERIUS, CHARLES W. HOOKER, R. G. HOSKINS, J. E. HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, MARY L. MILLER, C. C. PFEIFFER, DORIS PHELPS, J. P. PRATT, E. C. REIFENSTEIN, JR., BORIS B. RUBENSTEIN, PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, EMMERICH VON HAAM, HAROLD WOOSTER.

ADRENALS

ADLER, E. H., AND S. B. ABRAMS.

A case of Addison's disease associated with primary amenorrhea. *Am. J. Obst. & Gynec.* 45: 123. 1943.

The history, physical, laboratory, and X-ray findings of a case of Addison's disease with associated amenorrhea in a woman aged 26 are presented. It was thought that the patient reached adolescence with normally developing pituitary and gonads. The disease probably began at this time. The absence of both estrogen and gonadotropin in the urine proved the presence of a pituitary deficiency. The failure of mature development of the gonads in this case was believed to be due to failure of the basophile cells of the anterior lobe of the pituitary caused secondarily by their receiving inadequate stimulation from the adrenals. The patient's response was fairly good to the administration of 9 gm. of sodium chloride daily, along with a high carbohydrate, high vitamin diet.—*E.C.H.*

HUIZENGA, L. A., B. L. BROFMAN AND C. J. WIGGERS.

Ineffectiveness of adreno-cortical preparations in standardized hemorrhagic shock. *Proc. Soc. Exp. Biol. & Med.* 52: 77. 1943.

Using a method of hemorrhagic shock which produced irreversible changes in about 85% of dogs, it was observed that of 17 untreated dogs, only 4 or 23.5% recovered on reinfusion of the withdrawn blood. Of 20 animals treated with adreno-cortical preparations, 5 or 25% recovered, after the same experimental procedure. These observations fail to support the claims that cortical extracts exert a preventive or remedial influence in hemorrhagic shock.—*C.W.T.*

KEPL, M., G. CALDWELL, AND A. OCHSNER.

Use of adrenal cortical hormone in *Cl. welchii* infections in guinea pigs. *Proc. Soc. Exp. Biol. & Med.* 52: 25. 1943.

When 13 guinea pigs weighing 9 to 12 oz. were injected intramuscularly with 0.1 cc. of a culture of *Cl. welchii*, 12 died with an average survival time of 28.8 hr., with the classical picture of gas gangrene infection. Eleven animals were given 2 cc. of adrenal cortical extract, each cc. containing 25 dog units, one hour before infection and 6 injections of 2 cc. every 4 hours thereafter. Of these, 6 died with an average survival time of 30 hours. Six animals were given 3 doses of 4 cc. every 4 hours after infection. Five died with an average survival time of 47.5 hours.

When 0.2 cc. of the culture was administered with cortical extract death was again delayed in comparison to the controls. These experiments indicate that adrenal cortical hormone extract has a protective value in delaying death in *Cl. welchii* infections in guinea pigs.—*C.W.T.*

KOHLER, V., AND A. FLECKENSTEIN.

Treatment of ulcer with percortin. *Deutsch. Med. Wochenschr.* 68: 476. 1942.

Relief from pain in gastric or duodenal ulcer is obtained in 2–3 days of daily intramuscular injections of 20–35 mg. of desoxycorticosterone acetate. Case reports and roentgenograms illustrate the rapid healing. In all, 11 ulcer patients were improved by DOCA therapy after failure of bed-rest, warmth, diet, and atropine. The asthenic, hypotonic, vasolabile constitution of ulcer patients is considered to be correlated with adrenal cortical insufficiency and the effects of DOCA are through its systemic action in this deficiency and also by direct action on the gastrointestinal mucous membrane. Benefit is also noted in gastritis.—*G.A.E.*

SARASON, E. L.

Adrenal cortex in systemic disease. A morphologic study. *Arch. Int. Med.* 71: 702. 1943.

The adrenal glands of 110 patients were studied in an effort to correlate cortical changes with systemic disease. Cortical enlargement associated with depletion of lipoid or reversal of lipoid pattern was found associated with inflammatory diseases, cachexia, pemphigus and protracted emesis. Cortical enlargement with an increased amount of lipoid was encountered in cases of hypertension; the change was more striking when the hypertension was associated with primary vascular disease. The explanation of these changes is not at hand. No significant alterations were present in the series of cases of atherosclerosis. Extreme enlargement was found in 4 cases of erythroblastosis fetalis. This study serves to emphasize that the enlargement of the adrenal cortex and the depletion of lipoid are reflections of the metabolic disturbances associated with certain systemic diseases and not the direct effect of the latter. *Author's summary.* —*I.B.*

WEICHERT, URSULA.

Treatment of the so-called Röntgen sickness with desoxycorticosterone. *Strahlentherapie* 71: 127. 1942.

Treatment of patients with desoxycorticosterone resulted in almost all cases in immediate improvement. Röntgen sickness, which resembles Addison's disease in many ways, is considered as due to adrenal insufficiency and results from increased protein destruction by irradiation.—*D.A.M.*

ENDOCRINE GENERAL

ALLEN, E., AND L. B. DONALDSON.

The colostrum intradermal test for the diagnosis of pregnancy. *Am. J. Obst. & Gynec.* 45: 208. 1943.

The technic is described for the colostrum intradermal test for the diagnosis of pregnancy. Out of 164 known pregnant women, 13 cases with conflicting results were discarded. There were 151 cases considered in the calculation; of these the percentage of accuracy was 54.30. Of the nonpregnant cases, 87.65% was correctly diagnosed. The authors conclude that there was a difference either in potency in individual colostrum samples or a periodic change in individual sensitivity. Skin sensitivity apparently played a part in false or incorrect reactions. They also believe that further work should be done on the hormonal content of colostrum.—*E.C.H.*

BENSON, R. E., AND J. A. BARGEN.

Chronic ulcerative colitis as a cause of retarded sexual and somatic development. *Gastroenterology* 1: 147. 1943.

Fourteen patients in whom chronic ulcerative colitis of the streptococcic type developed between the ages of 7 and 12 years exhibited severe retardation of growth and development. All presented a diminished linear growth with poor development of genitalia and absence of most of the normal secondary sex characteristics. Discussed in detail are the influence of nutrition, chronic sepsis and infection, hepatic disturbances and endocrine changes in the production of their condition. In 3 patients urinary assay for pituitary gonadotropins was attempted, but no hormone was found. This suggested to the authors the possibility that in some instances of ulcerative colitis there may be secondarily an altered function of the pituitary gland.—*T.H.McG.*

BROWN, W. E., AND V. M. WILDER.

The response of the human uterus to epinephrine. *Am. J. Obst. & Gynec.* 45: 659. 1943.

The action of epinephrine was studied on three types of human uteri: (a) laboring uteri with spontaneous rhythm, (b) puerperal uteri exhibiting spontaneous rhythm, and (c) puerperal uteri with an oxytocically induced rhythm. The drug was usually given intravenously in the form of epinephrine solution 1:1000 in saline in one to two minim amounts. Observations were made by direct manometric methods. A premature contraction of the uterus was caused which was followed by a short latent period but without evidence of relaxation. Any apparent relaxation following epinephrine was always preceded by a period of increased activity. There was no difference in response in the spontaneously contracting uterus and the uterus with the oxytocically induced rhythm. There was no drop in tone indicating a relaxation. The use of epinephrine in disturbances of uterine contraction such as Bandl's ring, retraction rings, etc., is not recommended. It may be dangerous in these patients because of fatigue, dehydration and shock.—*E.C.H.*

CREEVY, C. D.

Hormones and carcinoma of the prostate. *Journal Lancet* 62: 452. 1943.

The author recommends that estrogen (stilbestrol orally, estradiol intramuscularly or as implanted pellets) be tried in every case of prostatic cancer not confined to the gland itself and that, if they fail, castration be performed.—*C.W.T.*

GARDNER, W. U., AND C. A. PFEIFFER.

Influence of estrogens and androgens on the skeletal system. *Physiol. Rev.* 23: 139. 1943.

Gonadal tissues and the steroid hormones elaborated therein exert influences on bone proliferation and possibly on the mechanism regulating calcium levels. In certain species sclerosis of cartilaginous matrix, proliferation and ossification of medullary osteogenic tissues are augmented by estrogens, serum calcium levels being, however, unchanged. Androgens tend to prevent excessive osseous growth in mammals treated with estrogens. It is assumed that stimulation of medullary proliferation by estrogen is due to their effects on osteoblasts or on the differentiation of osteoblasts. Large amounts of estrogens inhibit growth of cartilage and bone and longitudinal osseous growth. Small amounts of androgen augment rate of longitudinal growth of the skeleton. The reviewers suggest that steroid hormones may find practical use in senile osteoporosis, healing of fractures or augmentation of somatic growth in certain hypogonadal patients. —*D.A.M.*

GEIST, S. H., AND SALMON, U. J.

Present status of endocrine diagnosis and therapy in gynecology. *Clinics* 1: 1197. 1943.

Endocrine therapy in the human female has undergone considerable change in the past few years. The literature dealing with the subject has assumed such vast proportions and appears frequently to be so contradictory that the practicing physician finds it difficult, if not impossible, to keep himself informed of all the new advances reported. The authors conclude to the effect that estrogen, pregnandiol and gonadotropic hormone determinations are appraised from the point of view of their practical value to the clinician as an aid in diagnosis. The value of morphologic diagnostic studies, namely vaginal smears and endometrial biopsies, is discussed. The present status of the endocrine treatment of the menopause and amenorrhea is reviewed. The value of androgens in the treatment of functional dysmenorrhea, pre-menstrual tension, functional meno-metrorrhagia and frigidity is briefly detailed.—*I.B.*

GOODFRIEND, J. R., AND M. DANIEL.

The histidine test (Kapeller-Adler) in the diagnosis of pregnancy. *Am. J. Obst. & Gynec.* 45: 140. 1943.

An accuracy of 91% was obtained with the histidine test on the urines of 56 pregnant women. There were five errors on the urines of 72 nonpregnant women of childbearing age, no errors on those of 26 climacteric patients, nor on 6 males. There was thus an accuracy of 95% in all the control groups together. The authors believe that the results are encouraging enough to warrant further investigation of the Kapeller-Adler test as a rapid method in the diagnosis of pregnancy.—*E.C.H.*

GREENBLATT, R. B.

Intracyclic bleeding. *Am. J. Obst. & Gynec.* 45: 299. 1943.

The ovulation syndrome of intracyclic bleeding or of midmenstrual pain was alleviated in six women, whose ages ranged from 19 to 39 years, by the use of chemically pure androgenic substance. The administration of testosterone propionate parenterally in 10 to 25 mg. doses at weekly intervals was effective, as was methyl testosterone orally in 5 to 10 mg. doses throughout the intermenstruum.—*E.C.H.*

GREENHILL, J. P.

Endocrine problems in gynecologic practice. *Med. Clin. North America* 27: 27. 1943.

This is a general outline of the subject, including physiologic considerations of pituitary and ovarian hormones, chorionic gonadotropin and the male sex hormone. Treatment of common gynecologic conditions as dysmenorrhea, amenorrhea, menorrhagia, premenstrual tension, the menopause and senile vaginitis receives practical comment. The author concludes with a note of caution against the indiscriminate use of hypodermic treatment in every endocrine disorder. The primary requisite is a correct diagnosis in which cancer must be ruled out in all cases of irregular bleeding. It is then that the proper endocrine product for the disturbance under consideration may be selected.—*I.B.*

HAMBLEN, E. C.

Endocrine therapy in gynecology and obstetrics. *Am. J. Obst. & Gynec.* 45: 147, 1943.

A review article. The hormonal agents used in gynecology and obstetrics may be grouped thus:

(1) crystalline steroids which are hormones of the gonads and adrenal cortex or their derivatives and certain nonhormonal synthetic chemicals with endocrine-like properties; (2) extracts of protein or protein-like nature derived from the pituitary and thyroid glands and from certain body fluids.

The steroids are comprised of: estrogens, androgens, progestational principles and adrenal steroids. The 2 groups of estrogens are the hormonal and the nonhormonal steroids. The former are estradiol, estrone and estriol. The first two are usually administered intramuscularly in oil, and estriol is given orally. The best known of the nonhormonal estrogens is diethylstilbestrol, usually given by mouth. Estrogens have also been applied locally to the vaginal and nasal mucosae, by dermal inunction, and by subfascial implantation of sterile pellets. The indications for treatment with estrogens and the dosages in the following conditions are discussed: hypo-ovarianism originating in adolescence, anovulatory failure in adolescence, intercurrent ovarian failure during the preproductive epoch, the climacteric, pregnancy and the puerperium and other conditions not necessarily gynecologic in origin. The possibility of the carcinogenic rôle of estrogens should be remembered.

Up to the present time, no clinical studies have been reported which definitely associated any functional syndrome of the female with insufficient androgenic function; therefore, at present, androgenic therapy in the female is contraphysiologic.

Progestational principles, consisting of progestin, progesterone, and anhydro-hydroxy-progesterone, are discussed as to their efficacy in the therapy of abortion, dysmenorrhea, "afterpains" and prolonged or excessive functional uterine bleeding.

The indications for desoxycorticosterone acetate, the most widely used of the cortical steroids, are vomiting of pregnancy and preoperative preparation and postoperative care of patients requiring adrenal surgery.

The extracts of protein or protein-like nature are comprised of gonadotropins and thyroid substance. The gonadotropins may be divided into three groups, depending upon their sources: (1) pituitary, extracted from the pituitary gland itself; (2) chorionic, extracted from pregnancy urine; (3) equine, extracted from the serum of pregnant mares.

As yet, there are no extracts of the anterior pituitary which yield satisfactory clinical results.

In general, gonadotropic therapy has several limitations and undesirable qualities. However, equine gonadotropin may be used in adolescent estrogenic failure; and in patients with anovulatory failure, cyclic 1-2 gonadotropic therapy may be used. This embraces the administration of equine gonadotropin in daily doses of 400 I.U. for 10 days beginning on the fifth day of the cycle, and beginning on the fifteenth day of the cycle, chorionic gonadotropin is given intramuscularly in daily doses of 500 I.U. for ten days.

For therapy of relative corpus luteum failure, the suggested dosage of chorionic gonadotropin is 500 I.U. daily for ten days beginning on the fifteenth day of the cycle.

The use of thyroid substance in functional uterine hemorrhage, in endocrine sterility and in abortion is discussed.—*E.C.H.*

HAMBLEN, E. C., D. V. HIRST AND W. K. CUYLER.

Effects of estrogenic therapy upon ovarian function. II. When employed during anovulatory cycles. *Am. J. Obst. & Gynec.* 45: 513. 1943.

Sixteen patients were studied ranging in age from 15 to 35 years, who had presumed anovulatory ovarian failure predicated upon the occurrence of episodes of estrogenic bleeding. Endometrial biopsies were done prior to, during, and after therapy. The following treatment was given: estradiol was administered intramuscularly, and estriol glucuronide and diethylstilbestrol were given orally. Their administration was cyclic, i.e., from the fifth to the fourteenth day of the cycles of five patients, and from the fifth to the twenty-fourth days of the cycles of eleven patients. Daily dosages varied: those of estradiol benzoate from 0.33 to 0.67 mg.; those of estradiol dipropionate 2.5 mg. every other day; those of estriol glucuronide from 1800 to 4800 oral units; and those of diethylstilbestrol from 1 to 3 mg.

Twenty-two of the 26 biopsies studied during therapy continued to be of estrogenic nature. The four progestational responses in two patients were related to prolonged therapy with estriol glucuronide and were judged to be evidence of intercurrent recoveries of function.

It was concluded that the cyclic administration of moderate doses of hormonal and nonhormonal estrogens resulted in no direct stimulational effects upon ovaries in anovulatory failure. Such therapy regulates the cyclicity and duration of flowing probably by direct alterations in the

functional capacities of the endometrial vessels. The ultimate salvage, which has been related to the cyclic combined therapy with estrogen and progesterone, seems to be dependent upon the one-two sequential use of and the synergism existing between estrogen and progesterone.—*E.C.H.*

HEIMAN, J.

Comparative effects of estrogen, testosterone and progesterone on benign mammary tumors of the rat. *Cancer Research* 3: 65. 1943.

Progesterone inhibits growth of the adenomatous portion of spontaneous rat mammary fibro-adenoma and reduces the percentage of takes of auto- and homotransplants. The tumor stimulating effect of 2.5 mg. estrogen is not inhibited by 18 mg. progesterone although smaller doses of estrogen are inhibited by 18 mg. progesterone. Progesterone alone does not affect fibromas in castrated females and normal males but inhibits growth of the glandular portion of adenofibromas in castrated males. Combinations of progesterone and testosterone were somewhat more effective than progesterone alone in reducing percentage of takes in transplants and in inhibiting growth of the glandular fraction. Large doses of progesterone or testosterone were necessary to neutralize the stimulating effect of estrogen on growing fibro-adenoma. Rat fibroma, myxoma and sarcoma were not inhibited by progesterone. Progesterone does not inhibit growth of fibro-adenomas in pregnant rats, possibly because of high estrogen levels.—*D.A.M.*

HOFFMAN, MAX H.

Intersexual manifestations of nonendocrine origin. *Journal Lancet* 62: 446. 1943.

The case of a 16 year old boy with several abnormalities in his secondary sex characters including the lack of beard growth, the feminine type of pubic hair distribution and enlarged breasts is presented. Studies of the urinary sex hormone secretions showed low levels of both androgens and estrogens. The author suggests that the disturbed mechanism in the sex character development of this boy must be on a chromosomal basis rather than of endocrine origin.

A case of marked hirsutism of nonendocrine origin in a woman 48 years old was described. The beard and mustache was very heavy and dark. There was also a rather heavy growth of hair on the extremities and abdomen of the masculine type. Breast development was normal. Postmortem examination showed that the right adrenal gland contained a greyish white tuberculous mass located in the medulla. The cortex was normal on macroscopic and microscopic examination. The pituitary, thyroid and ovaries were normal.—*C.W.T.*

JACOBY, A., AND B. RABBINER.

Clinical evaluation of testosterone propionate and methyl testosterone in dysmenorrhea and menometrorrhagia. *Am. J. Obst. & Genec.* 45: 697. 1943.

Eighteen patients with dysmenorrhea and nine patients with menorrhagia and menometrorrhagia were treated with testosterone propionate and methyl testosterone. Complete relief of symptoms was experienced by four and improvement by eight of the dysmenorrhea patients and complete relief by six and improvement by two of the menometrorrhagia patients. In practically all cases there was a recurrence of the original ailment after discontinuation of treatment at varying intervals. Oral androgenic therapy, when given in adequate dosage, produced the same result as parenteral treatment.

It is believed that the basis of the alleviation of dysmenorrhea by male hormone in smaller doses could be the reduction of excessive contractions of the uterus. Again, the inhibition of the uterine contractility has been shown to decrease the volume of blood flow to the uterus, and thus the beneficial results on the menometrorrhagia. The recurrence of symptoms after cessation of therapy would seem to indicate that no permanent alteration in the patient's hormonal balance had been effected by the therapy of the duration described here.—*E.C.H.*

LUBIN, S., AND R. WALTMAN.

Missed abortion. An analysis of results following conservative management. *Am. J. Obst. & Gynec.* 45: 89. 1943.

A series of eighteen cases of missed abortion is presented where the dead ovum was retained for at least 28 days and up to 196 days. The ages of the patients ranged from 20 to 44 years. There were no alarming symptoms of retention, as toxemia, hemorrhage or infection. There was no maternal mortality and in only one case was there any morbidity. The Friedman test was found to be of value only when negative.

The change in one case in the pH of the vaginal secretions from acid to alkaline with the death of the fetus believed to indicate a fall in the estrogenic titer in the blood. It is thought by

some to be of greater value than the Aschheim-Zondek test in determining fetal death.

The hormonal method of induction may be attempted with estrogens first, to be followed later by pituitrin. Two of the authors' cases were given 1 mg. of stilbestrol daily for four or five days with good results. The only indication for surgical intervention was active bleeding.—*E.C.H.*

McKelvey, J. L.

Irregular shedding of the endometrium. *Journal Lancet* 62: 434. 1942.

The problem of irregular shedding of the endometrium in relation to an understanding of the menorrhagias is discussed. In a study of a small series of cases, it has been observed that estrogen and androgen excretion levels have been normal. Pregnandiol, however, continues to be excreted after the onset of menstruation. Thus irregular shedding is characterized by an abnormal prolongation of the excretion of pregnandiol.—*C.W.T.*

Millen, R. S., and K. Shepard.

The association of vaginal bleeding to organic pathology and the endometrial pattern in the decades before the menopause. *Am. J. Obst. & Gynec.* 45: 812. 1943.

From a study of 3956 women with abnormal vaginal bleeding during the reproductive period, the suggestion is made that this complaint is not caused by any one organic pathologic condition or endometrial pattern, but rather it is a symptom often associated with pelvic disorders. These may be complications of pregnancy, cancer, benign tumors, erosions of the cervix and malpositions of the uterus. Each pelvic lesion is classified with its associated endometrial pattern. Abnormal bleeding may also occur in patients with grossly normal pelvic organs with the endometrial pattern of one of the normal cyclical phases, which are classified as follows: early follicular, follicular, early corpus luteum, and premenstrual. The atrophic, hyperplastic, hypertrophic, and mixed patterns, and those of adenomyosis and chronic endometritis are discussed briefly.—*E.C.H.*

Rea, Charles E.

An evaluation of the clinical use of male sex hormone. *Journal Lancet* 62: 449. 1942.

A brief review of the physiological and pharmacological action of testosterone was given. The chief indication for the use of male sex hormone is in the replacement therapy of the prepuberal and postpuberal castrates.—*C.W.T.*

Reddoch, J. W., and W. B. Wiener.

Stilbestrol in the termination of pregnancy. *Am. J. Obst. & Gynec.* 45: 343. 1943.

Twenty-eight patients, in whom for one reason or another, induction of labor seemed desirable, received stilbestrol with a total dosage of from 6 mg. to 720 mg. Beginning about 3 hours after the oil and enema, pitocin in small doses was given routinely except in patients in whom labor had started. The criterion for success was labor within 24 hours after the last dose of stilbestrol on the day of the induction. Of the 28 cases there were five missed abortions, or abortions with five successes; 22 in whom an effort was made to aid in the induction by using stilbestrol with 9 successes, or 41%. There was one case of uterine inertia who was finally delivered with Dührssen's incisions.

There was no appreciable effect on lactation in any of the cases. As a part of the technic of medical induction, the use of stilbestrol was not entirely justified in the author's hands.—*E.C.H.*

Ross, R. A.

The involutional phase of the menstrual cycle (climacteric). *Am. J. Obst. & Gynec.* 45: 497. 1943.

Forty-one women during the climacteric or artificial menopause were studied. The fact is emphasized that this age should not be considered a disease, nor should it be considered as entirely dependent and definite with ovarian failures. The hormonology of the climacteric is discussed and may be summarized briefly: refractivity of the ovary to pituitary stimulation, failure of ovulation, gradual lag in the response to follicle stimulation with receding waves of estrogenic output, a temporarily uninhibited pituitary with varying adrenal and thyroid stimulation.

The complications of the climacteric are: irregular bleeding, vasomotor phenomena, abnormal psychic states, thyroid disorders, pelvic relaxation, and systemic breakdowns. These should be investigated before any therapy is attempted. This should consist of psychotherapy, correction of irregular bleeding, systemic treatment, necessary repair work, mild sedation and organotherapy. Estrogens are recommended in small doses by mouth. Diethylstilbestrol, if used,

should not exceed 1 mg. a day. Emmenin in doses of 480 to 960 day oral units may be given. Androgen therapy is contraindicated.—*E.C.H.*

SAMUELS, LEO T.

Important advances in the physiology of the sex hormones. *Journal Lancet* 62: 419. 1942.

A brief review of recent literature concerning the following topics is given: The primary changes in tissues after estrogen stimulation. The general metabolic changes produced by the androgens. The rôle of the liver in the intermediary metabolism of steroid hormones. The extragenital origin of sex hormones. The large variety of compounds produced from the sex hormones during their intermediary metabolism. The rôle of the steroid hormones in the genesis of tumors. —*C.W.T.*

SCHWARTZ, R. M.

Pathology of postmenopausal bleeding. *Am. J. Obst. & Gynec.* 45: 522. 1943.

The pathology of 114 specimens from women past the menopause or over 50 years of age who had anomalous bleeding is reviewed. The percentage of benign lesions of the endometrium or cervix is 56.9, and the percentage of malignancy is 43.1 Endometrial hyperplasia represented 7.0% of the total. The cause for bleeding could not always be determined. It is stated that if menstruation and ovulation together end abruptly, the endometrium will be of the atrophic type. If the terminal cycles are anovulatory, the hyperplastic pattern may exist even in the absence of postmenopausal bleeding. After estrogenic production ceases, the pre-existing hyperplasia may show marked regressive changes in the epithelium and stroma.—*E.C.H.*

SIEGLER, S. L., AND D. BAUER.

An evaluation of the pregnandiol complex as an index of ovarian and uterine function. *Am. J. Obst. & Gynec.* 45: 277. 1943.

Studies were done on the following women to evaluate pregnandiol excretion as a diagnostic index of ovarian and uterine function: 1. Controls; (a) 4 with normal menstrual cycles; (b) 2 with primary sterility; 2. Before and after hormone administration: (a) 6 with amenorrhea; (b) 4 with cyclic anovulatory menstruation; (c) 1 case of secondary sterility (2 previous abortions) and normal cycles; (d) 1 with bilateral salpingo-ophorectomy, uterus intact; (e) 1 with supracervical hysterectomy, ovaries intact; (f) 1 with complete vaginal hysterectomy, ovaries intact; (g) 1 with panhysterectomy. Sodium pregnandiol glucuronidate was estimated according to the gravimetric method of Venning. Endometrial biopsies were done concurrently.

It was concluded that excretion of pregnandiol is not a positive index of ovulation nor of progesterone metabolism. It is often complementary to endometrial biopsy and basal body temperature studies, but it is impracticable for diagnosis in clinical practice because of its time-consuming nature and the fact that urinary specimens for 10 to 14 consecutive days must be examined to find a relative level of progesterone metabolism for one cycle.

The authors found that estrogens augment the metabolism and utilization of progesterone when the hormones are given simultaneously to an estrogen-primed uterus. Pregnandiol and endometrial biopsy studies did not show a consistency of administered gonadotropic hormones in establishing a biphasic ovarian response. The endometrium was found not to be necessary for the metabolism of endogenous and exogenous progesterone. It is suggested that some at present undefined hormone influences will prove to be important in the metabolism of progesterone and pregnandiol excretion.—*E.C.H.*

SMITH, O. W., G. V. S. SMITH AND S. SCHILLER.

Clinical experiments in relation to the excretion of the estrogens. III. Urinary estrogens in a normal menstrual cycle and in a case of essential dysmenorrhea. *Am. J. Obst. & Gynec.* 45: 15. 1943.

Urinary estrogens were done during one cycle on a 37 year old woman who had had a normal menstrual history since her menarche and had had two normal pregnancies. Results indicated that some luteal activity normally precedes ovulation and that estrogen degradation plays a physiologic rôle in the regulation of cyclic ovarian secretion.

Similar studies were done for three cycles on a 26 year old unmarried woman who had had fairly regular but consistently painful periods since her menarche. There had been no pelvic or organic abnormality to account for the pain in the five years that she had been under observation. Her urinary estrogens were very low, due to a comparative deficiency in luteal effect throughout the cycle. The shift in steroid metabolism at the start of the flow, pointing to a sudden increase in the rate of estrogen degradation, was less marked in this patient than in the normal.

It was thought that this might be significant in relation to the indicated subsequent comparative deficiency in normal growth and maturation of the ovarian follicle.

The above findings and the results of therapy with estrogens suggest an as etiologic factor in this case of dysmenorrhea the subnormal luteal activity with resulting incomplete premenstrual preparation.—*E.C.H.*

SMITH, O. W., G. V. S. SMITH AND A. G. GAULD.

Clinical experience in relation to the excretion of the estrogens. IV. The effect of veratrum viride upon urinary estrogens in pre-eclampsia. *Am J. Obst. & Gynec.* 45: 23. 1943.

Studies were done on a 23 year old woman with severe pre-eclampsia. Treatment with progesterone and estrogen and adrenal cortical extract showed that the administered hormones were being destroyed rather than utilized for the establishment of a more normal metabolism of the estrogens.

The administration of veratrum viride alone for four days markedly affected the excretion of estrogen metabolites by the temporary vasodilatation caused by this drug. The findings indicated a sudden decrease in degradation and increased metabolic conversion of the estrogens. The hormonal effects lasted no longer than the clinical.

It is believed that a reciprocal relationship exists between the vascular system and female sex hormones. An adequate vascular supply is just as important for the proper production and metabolism of the placental and ovarian steroids as adequate sex steroids are for genital vascularity. Thus, it would seem that any mechanical or organic disturbance which affects adversely the the blood supply to the placenta may be one of the primary causes for pre-eclampsia and eclampsia.

Therapy is suggested either as replacement therapy with estrogen and progesterone or by directly combating the vasoconstriction. The limitations of the former are apparent in this case. The principal drawbacks to the latter are the relatively short duration of the action of veratrum and its toxic side effects. The possibility of supplementing sex steroid therapy with veratrum viride should be investigated.—*E.C.H.*

SOULE, S. D.

A clinical trial of ethinyl estradiol. *Am. J. Obst. & Gynec.* 45: 315. 1943.

A series of 30 postoperative, postradiation and natural menopause patients were treated with ethinyl estradiol in daily doses of 0.05 mg. It was found to be therapeutically satisfactory and well tolerated in 93% of the cases. It is the most active oral estrogenic hormone used to date by the author.—*E.C.H.*

SZEGO, C. M.

Methods of measurement of the naturally occurring sex hormones. *Journal Lancet* 62: 423. 1943.

A review of methods of measuring estrogens, androgens, progesterone, pregnandiol and chorionic gonadotropin.—*C.W.T.*

TAYLOR, H. C., JR., F. E. MECKE AND G. H. TWOMBLY.

Estrogen and 17-ketosteroid excretion in patients with breast carcinoma. *Cancer Research* 3: 180. 1943.

Spontaneous excretion of estrogens and 17-ketosteroids was studied in numerous patients with or without various coexisting endocrine disorders. No abnormal values referable to breast cancer were found. When estrone, testosterone propionate and progesterone are injected into women, definite alterations occur in the rates of estrogen and 17-ketosteroid excretion in the urine and in the duration of the menstrual cycle. The exact alterations which occur depend to a considerable extent on the time of the cycle in which the hormone is administered. Certain contrasts in the response to hormone injection were noted in a seven month study of one woman with breast cancer and one normal control. Differences in response reflect physiologic differences and suggest clinical methods whereby predisposition to breast cancer may be sought.—*D.A.M.*

WERNER, S. C.

A quantitative study of the urinary excretion of hypophyseal gonadotropin, estrogen, and neutral 17-ketosteroids of normal men. *J. Clin. Invest.* 22: 395. 1943.

The subjects of these tests were 5 "healthy" men, two of whom, however, were undergoing psychologic study at the time the analyses were made. Determinations were carried out in 1 patient for a month, and in all others for not less than 3 months. While the values for the 17-ketosteroids of the urine varied rather widely from patient to patient, for any single individual

they were reasonably constant from day to day and from week to week. Marked fluctuations were noted in urinary gonadotropins and estrogenic substances, which could not be related to each other, to 17-ketosteroid output, or to physiologic activity. No evidence whatsoever of any cycle in the excretions of these hormones was observed.—*T.H.McG.*

GONADS

AREY, L. B.

The nature and significance of the grooved nuclei of Brenner tumors and Walthard cell islands. *Am. J. Obst. & Gynec.* 45: 614. 1943.

The endocrine interest to this article lies in the author's statement that unpublished evidence of his indicates that the Brenner tumor is derived from the germinal epithelium of the ovary. The possibility of estrogenic output, therefore, should be investigated.—*E.C.H.*

BARRINGER, B. S.

Treatment of prostatic carcinoma. *Bull. New York Acad. Med.* 19: 417. 1943.

The author concludes that orchidectomy and stilbestrol treatment (5 mg. daily) should be the treatment in all cases of prostatic carcinoma. This therapy should be preceded by transurethral resection if urinary retention is a dominant factor. Transurethral resection is not necessary to establish diagnosis, aspirational biopsy being preferred. If the carcinoma is small and confined to the prostate and peri-prostatic region, radiation or total prostatectomy should be considered. Stilbestrol therapy is of definite benefit in controlling pain, causing some recession of prostate growth and improvement in general condition of the patient. It rarely has any effect on bone metastases.—*D.A.M.*

CAMPBELL, H. E.

Incidence of malignant growth of the undescended testicle. A critical and statistical study. *Arch. Surg.* 44: 353. 1942.

By critical analysis of available data, the author concludes the undescended testicle is more susceptible to malignancy than is the scrotal and that the abdominal is more liable to malignant disease than the inguinal testis. The ratio of malignancy in the inguinal testis to that of the abdominal testis is 1 to 4. Analysis shows also that about 1 abdominal testis in 20 shows malignant change as compared to 1 in 80 inguinal.—*D.A.M.*

FERRIS, D. O.

Tumors of the testis: Correlation of pathologic characters with excretion of hormone in the urine. *Clinics* 1: 1026. 1943.

Tumors of the testis are rare, and almost all are malignant. Two types of tumor, seminoma and teratoma, comprise almost all malignant tumors of the testis. All malignant tumors of the testis cause excretion of excessive amounts of gonadotropic principle in the urine. Twenty R.U. per liter of urine is the dividing point between normal and excessive amounts. The test must be quantitative and the best technic is that of Frank. The best routine on the first analysis is to test for 25, 40 and 66 R.U. of hormone per liter of urine. Orchidectomy and subsequent extensive irradiation seem to be the best treatment. The survival rates compare quite favorably with results obtained in the treatment of malignant lesions elsewhere in the body. *Author's conclusions.—I.B.*

FOX, R. A.

Brenner tumor of the ovary. Case reports, discussion and bibliography. *Am. J. Path.* 18: 223. 1942.

Four instances of Brenner tumor are added to the 166 found in the literature. In 3 of the new cases and in 10 of those previously described, the tumors were bilateral and varied in size from tiny nodules to masses as large as a man's head. They were entirely solid or occurred as nodules in the wall of an ovarian cyst. They consisted mainly of fibrillary connective tissue with small nests of polyhedral cells. Central cyst-like spaces were lined with radially arranged columnar cells and contained mucoid secretion.—*D.A.M.*

GNASSI, A. M., J. B. FAISON AND M. FELLMAN.

Granulosa cell carcinoma. Report of 2 cases. *Am. J. Roentgenol.* 47: 458. 1942.

Two cases are reported in which rapidly fatal granulosa cell tumors with metastases occurred in women during the reproductive age. Treatment and surgery *are* discussed.—*D.A.M.*

GOLD, S.

Oestrogen therapy in testicular hypofunction. *Canad. M. A. J.* 48: 231. 1943.

Three patients with varying degrees of impotence due to testical hypofunction were treated with male and female sex hormones and sodium

cacodylate. The author is inclined to believe that the improvement in potency 2 weeks after the injection of the sodium cacodylate was due to both the residual effect of the estrogenic hormone and the period of abstinence. Precordial pressure was frequently experienced by the patient during coitus while under treatment with the sex hormones, male and female. This precordial pressure was absent after the treatment with sodium cacodylate, an observation which justifies the suggestion that sex hormone therapy in elderly males may have a predisposition to cardiospasm following physical exertion, since neither the hormones alone nor the sexual exertion alone produced the pressure sensation over the precordium. The effect of the estrogenic hormones on the libido and potency was found to be quicker and more intense than that of testosterone propionate, in the stated doses.—*Biol. Absts.*

HAMBLEN, E. C., D. V. HIRST, AND W. K. CUYLER.

Effects of estrogenic therapy upon ovarian function. I. When employed during normal menstrual cycles. *Am. J. Obst. & Gynec.* 45: 268. 1943.

Thirty healthy women with normal ovarian function were treated contraphysiologically with moderately small daily doses of hormonal estrogens: estrone 0.2 to 0.4 mg.; estradiol benzoate 0.33 mg. to 0.67 mg.; estradiol dipropionate 1.5 mg.; estriol glucuronide 450 oral units to 2400 oral units; and diethylstilbestrol 1 to 6 mg. Sixty-one cycles of therapy were administered during the first half of the ovarian cycle, i.e., from the fifth to the fourteenth day inclusive. Fifteen cycles of treatment extended from the fifth to the twenty-fourth day inclusive. Eight cycles of treatment were given during the last half of the cycle, i.e., from the fifteenth to the twenty-fourth day inclusive. Endometrial studies were made prior to, during, and after the cessation of the treatment. Sodium pregnandiol studies were done on nine patients before and during treatment.

It was found that estradiol dipropionate, when given intramuscularly in adequate amounts, depressed corpus luteum function. The other hormonal estrogens did not do so, presumably because of insufficient dosage. Diethylstilbestrol, even in moderately small oral doses, depressed corpus luteum function equally as much as did estradiol dipropionate. This was the only direct effect of estrogenic therapy on the ovarian level of function; it was not cumulative and did not persist after therapy. The definite and quantitative alterations in the menstrual cycle which were observed during therapy with estrogens given in larger doses probably resulted from action directly on the endometrium.—*E.C.H.*

JUROW, H. N.

Cyclic variations in the cervix of the guinea pig. *Am. J. Obst. & Gynec.* 45: 762. 1943.

Fifty-three normally cyclic virgin female guinea pigs were used for this study from one to three months after maturity had been reached. Vaginal smears were taken during various stages of the cycle and stained with hematoxylin and eosin. Animals were sacrificed at various stages, and histological studies made of the vagina, cervix, uterus and ovaries. It was found that a definite cyclic change occurs in the cervix during the estrous cycle, which followed closely the variations present in the other parts of the genital tract, especially the vagina. These cyclic changes were felt to be dependent on the hormonal cycle. —*E.C.H.*

KUHN, C. L.

Ovarian autografts. *Am. J. Obst. & Gynec.* 45: 704, 1943.

This is a report of 38 cases of ovarian autografts done in an attempt to supply varian secretion to those patients in whom surgical removal of both ovaries was necessary because of some nonmalignant ovarian disease. Multiple (from 8 to 16) thin-sliced grafts from ovarian cortex into rectus mucle are recommended. These grafts functioned when transplanted into rectus muscle as shown by menstrual activity usually for years in all cases with an intact uterus, and by microscopic demonstration of corpora lutea in grafts excised one and two years after implantation. Patients with an intact uterus tended to have higher urinary estrogen levels.

Of the 26 patients who were followed 65% showed relief from hot flushes and did not require estrogenic therapy. The choice between ovarian autografts and estrogenic therapy is a matter of judgment for the individual surgeon. —*E.C.H.*

MACK, H. C.

The glycogen index in the menopause. A study of certain estrogen functions based on a new method of staining vaginal smears. *Am. J. Obst. & Gynec.* 45: 402. 1943.

The iodine vapor method of staining vaginal smears is described as a rapid and simple means for the determination of the specific glycogen response to estrogenic activity in the human subject.

This method was used in studying 130 postmenopausal women ranging in age from 33 to 97 years to determine the incidence of glycogen poverty, and the smears were graded according to glycogen content. The incidence of the 4 glycogen grades was calculated according to age, duration of the menopause, and the nature of the climacteric, whether spontaneous or artificially induced. The persistence of variable amounts of vaginal glycogen in these women gave additional evidence that estrogen was continuing to be elaborated by the ovary or extragenital sources.

It is suggested that there may be "antihormonal" factors present in local and systemic (febrile states and vaginitis) which prevent the metabolic activity of estrogen and thus cause glycopenia.

The clinical usefulness of vaginal smear methods, including the one described here, is at present limited largely to the control of estrogen therapy in vaginitis and to investigations of potencies of commercial estrogens as judged by their effect on women with advanced glycopenic vaginal atrophy.—*E.C.H.*

NOVAK, J.

Testicular tubular adenoma in two sisters. *Am. J. Obst. & Gynec.* 45: 856. 1943.

Two cases of benign testicular tubular adenoma in two sisters are reported. Both patients looked and felt perfectly feminine, although the gonads consisted mainly of testicular tissue; the ovarian tissue was represented only by islands of ovarian stroma. Each sister had female external genitalia, a vagina, but no or almost no uterus and only a tiny tubal rudiment. Investigation showed that several other members of the family were affected with pronounced sexual abnormalities, the hereditary taint apparently having been transmitted from the grandmother to her children and grandchildren.

The gonads of these two cases were interpreted as ovotestes; the patients were intersexes. Embryologic facts and Goldschmidt's intersexuality theory are used to explain the origin of the malformation.—*E.C.H.*

ROTTINO, A., AND J. F. MCGRATH.

Hyperplasia and luteinization of ovarian stroma associated with masculinization. *Am. J. Obst. & Gynec.* 45: 863. 1943.

Two cases are reported of women, aged 36 and 38 years, respectively, with obesity, hirsutism and amenorrhea. One had hypertension. The removal of the ovaries produced no striking changes, although a primary complaint, headache, disappeared immediately in the hypertensive patient. The cause of the ovarian findings of stroma cell hyperplasia, theca cell proliferation and the clear cell islands is not known. The authors believe they do not represent a tumor but are a proliferative phenomenon induced by an endocrinologic imbalance affecting among other organs the ovarian stroma. Hyperplasia and luteinization of theca cells probably are manifestations of the same phenomenon modified somewhat by the proximity of these cells to the ovum. —*E.C.H.*

ROGERS, F. S.

Brenner tumor of the ovary complicating pregnancy. *Am. J. Obst. & Gynec.* 45: 896. 1943.

This is the fifth case of a Brenner tumor complicating pregnancy to be reported in the literature. It was removed without disturbance of the normal course of pregnancy.—*E.C.H.*

SIDDALL, R. S.

Sclerosis and related senile changes of the fallopian tubes. *Am. J. Obst. & Gynec.* 45: 785. 1943.

One hundred consecutive cases were studied which had had one or more definite fibroids in the uterus, at least one fallopian tube and one ovary removed and available for study, no salpingitis sufficient to distort the pathologic picture, no evidence of pregnancy and no irradiation treatment more than six weeks previously. It was found that with advancing sexual age, the fallopian tubes undergo certain changes consisting principally of a marked hypertrophy and sclerosis involving the connective tissue of the folds. Later, nonciliated and flatter cells replace the ciliated epithelium. This sclerosis, which was noted in 45% of cases with uterine leiomyofibromas, had little or no relationship to the size of the tumors. An investigation of another 100 cases corresponding to the above in every way except for the absence of fibroids, showed the condition in approximately the same proportion, the incidence increasing in both series with advancing age. Sclerosis of the fallopian tube was not related to previous pregnancies. Its incidence was

increased with the development of irregularities and anomalies of menstruation, and was most marked with the onset of the climacteric and afterwards. The same tendency was seen also with the histologic evidences (ovarian and endometrial) of sex hormone diminution. However, there were exceptions to the general rules.

Sclerosis was usually present in a small series of tubes associated with pregnancy, and therefore it is not an absolute barrier to pregnancy. However, it possibly might be a relative factor in sterility and also a cause of tubal pregnancy.

Doubt is cast upon statistical studies which apparently indicate a relationship between fibroids and certain other conditions, especially carcinoma of the uterine fundus.—*E.C.H.*

TAYLOR, H. C., JR., R. C. WARNER AND C. A. WELSH

The relationship of the estrogens and progesterone to the edema of normal and toxemic pregnancy. *Am. J. Obst. & Gynec.* 45: 547. 1943.

Five patients are reported who received either estrogen or progesterone immediately after delivery in an effort to prevent or modify the sodium loss and diuresis of the early puerperium. In three of these patients large doses of hormones were also given during pregnancy to determine if the sodium balance was in any way disturbed by such treatment. Controls were five patients previously reported who were studied during late pregnancy and the early puerperium without hormone administration.

The sodium balance of the five hormone treated patients showed, with certain exceptions, the general trends observed in the cases previously reported. These consist in a constant retention of sodium until the time of delivery with a negative balance appearing after parturition and reaching its greatest magnitude from the third to the fifth day. The days of greatest sodium loss correspond in general with the return of the urinary estrogen to nonpregnant levels.

The absence of the postpartum sodium loss in one and its apparent reduction in another case of normal pregnancy after estrogen treatment in the puerperium seemed to show that one of the causes of sodium and water retention in normal pregnancy is the high estrogen concentration characteristic of the body fluids during that period. It was seen that progesterone may contribute to this by the fact that in the case which was treated with this, the loss of sodium substance in the early puerperium was relatively slight. The effect of estrogens and progesterone on the prevention of diuresis and sodium loss in the puerperium of patients who had had toxemia of pregnancy was less convincing but still suggestive.

It was concluded that among several factors which cause edema in normal pregnancy, the most important is probably the physiologic influence of the estrogens and progesterone on the excretion of sodium and water. Additional factors are no doubt at work in the edema of toxemia but it must be remembered that when the pregnant woman develops toxemia she is already physiologically conditioned to retain water readily. In this indirect sense at least the estrogens and progesterone may contribute greatly to the clinical manifestations and course of the disease.—*E.C.H.*

TOPKINS, P.

The histologic appearance of the endometrium during lactation amenorrhea and its relationship to ovarian function. *Am. J. Obst. & Gynec.* 45: 48. 1943.

A total of 145 endometrial biopsies was done on 28 normal lactating women during the period of lactation amenorrhea. Of these, nine (6%) showed progestational changes, and all these were associated with the onset of the first menstrual flow. One hundred and thirty-six specimens (94%) showed estrogenic changes, and of these, twenty (15%) were hypoplastic.

It was concluded that the endometrium during lactation amenorrhea is not different from that found in amenorrhea caused by other factors; it shows diminished estrogenic stimulation. During lactation, the ovarian cycle is suppressed and ovulation does not occur. This is believed to be caused by suppression of the pituitary gonadotropic activity, due to prolactin or to some hormone of the lactating mammary gland.—*E.C.H.*

VEST, S. A., AND B. BARELARE, JR.

Androgens and the treatment of testicular hypofunction. *Clinics* 1: 1216. 1943.

The functions of the testicles, although incompletely understood, fall into 2 general categories: the formation of spermatozoa in the seminiferous tubules for reproduction, and the secretion of hormones, presumably from the interstitial cells responsible for certain body functions and morphologic characteristics. The effects of the synthetic androgen testosterone depend much upon its mode of administration, whether this be implantation, injection, ingestion or topical application. The authors discuss the treatment of

castrates and eunuchoids, deficiency after puberty, and the response to testosterone propionate in various other conditions in which it appears indicated. The effects of androgens on growth, vascular system, impotence and psychiatric conditions, as well as on the "male climacteric," prostatic hypertrophy, male sterility, cryptorchidism and delayed adolescence are discussed. The authors warn against assigning undue therapeutic properties to testosterone propionate in certain far reaching clinical states.—*I.B.*

WILLIAMS, T. J.

Hydatidiform mole and associated tumors of the chorion. *Am. J. Ost. & Gynec.* 45: 432. 1943.

A discussion of hydatidiform moles and their subsequent course with a review of 24 cases is presented. They may be benign, their passage complete and recovery uneventful. In about half of the author's cases, chorionic tissue remained in the uterine cavity or in the uterine walls, and caused persistent positive biologic pregnancy tests. The presence of a persistent positive test following a mole, abortion, or pregnancy justifies the diagnosis of viable chorionic cells; however, too much reliance should not be placed on a single negative test because of the frequency with which the test becomes negative and then later positive. It is the custom of the author, in the presence of a persistent positive test, to perform a curettage, and if a month or so later, the test is still positive, an abdominal exploration of the pelvis with hysterectomy is thought advisable.

The cases recorded here have been classed microscopically as synctial endometritis or synctioma (infiltration with synctium only), malignant mole or chorioadenoma (synctium, Langhans' cells and villi), or chorionepithelioma (Langhans' cells and synctium).—*E.C.H.*

WINTHER, N.

The endocrine factors in menstruation and its relation to dysmenorrhea. *Journal Lancet* 62: 428. 1943.

A study is reported concerning the effect of various hormones upon the estrogen and pregnandiol content of the urine of normal cyclic women. Gonadotropic hormone from PMS increased the output of estrogen but did not effect the excretion of pregnandiol. The administration of progesterone increased the output of pregnandiol but did not influence the output of estrogen. The administration of anhydro-hydroxy progesterone, orally, did not increase the output of pregnandiol. There was no correlation between the estrogen and pregnandiol levels and the symptoms of dysmenorrhea.

A controlled clinical study indicated that the benefits from the use of estriol glycuronide in the treatment of dysmenorrhea were no greater than with placebo. A combination of estrogen and progesterone given concurrently may give better results.—*C.W.T.*

HYPOPHYSIS

BARNETT, H. L., ANNE M. PERLEY AND P. HEINBECKER.

Influence of eosinophile cells of hypophysis on kidney function. *Proc. Soc. Exp. Biol. & Med.* 52: 114. 1943.

Two clinical cases are reported in support of the theory that the eosinophile cells of the anterior pituitary exercises a humoral influence on the kidney.—*C.W.T.*

GOLDZIEHER, M. A.

Diagnosis and treatment of pituitary disease. *Clinics* 1: 1069. 1943.

This is a rather comprehensive discussion of the subject in its various phases with 17 illustrative case histories. It is often more difficult to diagnose pituitary disease than most of the other endocrinopathies. The hypophysis is not only inaccessible to inspection or palpation in contrast to most other glands, but the symptomatology is also more varied and complex. Pituitary disease owes its protean character to the following 3 reasons: 1. The functional activities of the 2 lobes of the pituitary are multiple and may become dissociated in the course of disease, so much so that 1 or 2 of the varied activities are deficient while other functions remain unaltered. A combination of deficiency in one line with excessive activity in another is also noted. 2. The manifestations of disturbed pituitary function are produced often through the mediation of another endocrine gland, hence our attention is drawn to the secondary accomplice while the primary responsibility of the pituitary remains hidden. 3. Most of the essential metabolic processes are regulated directly or indirectly by the pituitary. Thus any disease of the gland is followed almost inevitably by metabolic disorders. However, the resulting symptoms may appear altogether unrelated to the primary glandular disease. The author classifies the various pituitary disorders

insofar as classification is made possible by clinical evidence. Dwarfism, infantilism, gigantism, cryptorchidism, secondary hypogonadism, disturbances of carbohydrate metabolism, obesity, pituitary leanness, Simmonds' disease, and disturbances of salt and water metabolism all are discussed with respect to diagnosis and treatment. Those interested in diseased of the pituitary would do well to peruse this contribution carefully.—*I.B.*

PAGE, ERNEST W.

Response of human pregnant uterus to pitocin tannate in oil. *Proc. Soc. Exp. Biol. & Med.* 52: 195. 1943.

Injections of pitocin tannate in oil were given to 22 women for the induction of labor at term and to 10 women whose labors were complicated by primary uterine inertia.

A graphic record of the response was obtained by means of the Lorand tocograph. In each case, the minimal effective dose of pitocin was determined before administering pitocin tannate in oil.

The latent period between the time of injection of pitocin tannate in oil and the onset of response was usually 8 to 10 minutes, or about twice as long as the latent period for pitocin. The ratio of minimal effective dose of the tannate to pitocin averaged 4 times the number of units, i.e. one unit of pitocin was equivalent to about 4 units of the preparation in oil. The duration of action was 3 to 4 times as long. It was suggested that the tannate preparation be used when a longer acting oxytocic is desirable. It possesses the same inherent dangers of ordinary posterior pituitary hormone.—*C.W.T.*

WALL, H. C.

A renal concentration test using solution of posterior pituitary. *Arch. Int. Med.* 71: 454. 1943.

A renal concentration test using solution of posterior pituitary is described. This test is applicable without the necessity of previously depriving the patient of water and in the presence of edema or ascites. The results obtained for normal subjects, for patients suffering from hypertension without impairment of renal function, and for patients who had impaired renal function compare favorably with the results obtained with the Fishberg and phenolsulfonphthalein tests. The advantages and contraindications are described. *Author's summary.—I.B.*

WERNER, S. C., AND R. WEST.

Nitrogen retention, creatinuria, and other effects of the treatment of Simmonds' disease with methyl testosterone. *J. Clin. Invest.* 22: 335. 1943.

Four patients having Simmonds' cachexia were treated with methyl testosterone in doses of 20 mg. 5 times daily. All of the patients showed renewed vigor, a gain in weight, a return of or increase in libido, and the reappearance of previously lost secondary sex characteristics. The authors emphasized the fact that seborrhea did did not occur, "suggesting that androgens act to produce seborrhea only after the skin has been prepared by some basic mechanism or mechanisms, which are wanting following hypophyseal failure." In 2 of the patients, careful metabolic studies were carried out. Nitrogen retention and creatinuria were observed routinely, the creatinuria appearing after a latent period of several weeks. The basal metabolic rate tended to rise; cholesterol values were depressed, sometimes to unusually low levels. Changes in serum proteins were questionable. Oral glucose-tolerance tests reverted to normal. Serum electrolytes and nonprotein nitrogen remained normal. No rise in urinary 17-ketosteroids was observed. It is suggested that, while methyl testosterone is a very incomplete substitution therapy in Simmonds' disease, the encouraging results from its use warrant further and more extended trial.—*T.H McG.*

PANCREAS

ALLAN, FRANK N.

Diabetes in 1942. *West Virginia M. J.* 39: 105. 1943.

The present status of diabetes is discussed and diagnosis and care are reviewed in regard to 100 patients. Of these, only 35 presented classical symptoms at time of diagnosis. Therapy included slight dietary restriction alone in 17, strict limitation in 23, diet and less than 30 U insulin in 41, and more than 30 U in 19. Age incidences of the different grades of diabetes are noted. The use of protamine insulin is discussed. Complications included acidosis in 9, retinitis in 6, neuritis in 6, and foot lesions in 4; associated obesity, hypertension, angina pectoris, gall stones, cirrhosis, pancreatitis, pregnancy, hyperthyroidism and adenomatous goiter are also noted as to incidence. One patient had extreme insulin resistance, together with local allergy to its injections; mild local allergies occurred

temporarily in several others. Insulin lipodystrophy occurred in 1 case.—*G.A.E.*

FREE, A. H., A. J. BEAMS AND V. C. MYERS.

Studies of the enzyme activities of duodenal contents as a means of evaluating pancreatic function. *Gastroenterology*, 1: 188. 1943.

Duodenal contents withdrawn at the end of each of 3 twenty-minute periods following the intraduodenal administration of 25 cc. of olive oil were analyzed for proteinase, amylase, and lipase activity. Eleven normal individuals and 4 patients with pancreatic disease, 9 with chronic diabetes mellitus, and 27 afflicted with various gastrointestinal disturbances were studied. In 8 of the 9 diabetic patients, there was a decrease in enzymic activity, amounting in terms of the normal to 54% for proteinase, 69% for amylase, and 70% for lipase. The ninth of these individuals showed a marked elevation of values, for instance, in the case of lipase, reaching 224% of normal.—*T.H.McG.*

MARTIN, H. E., AND A. N. WICK.

Quantitative relationships between blood and urine ketone levels in diabetic ketosis. *J. Clin. Invest.* 22: 235. 1943.

Through a study of urinary ketone excretion and blood ketone levels, the authors have approached the whole problem of the renal threshold for ketones. Thirteen diabetics in mild, purposefully induced ketosis, and 7 patients hospitalized for a spontaneously occurring acidosis of moderate to severe degree served as subjects for the study. As a result of plotting the urine against the blood values of the ketone bodies over a wide range of levels, the authors concluded that beta-hydroxybutyric acid is a "renal threshold substance" for which a blood level of 20 mg.% must be attained before any appreciable amount is found in the urine. When blood ketone levels were less than 20 mg.%, the urinary output of ketones was very low and largely due to the excretion of acetone. These experiments also showed a general impairment of urinary excretion of ketones with kidney failure. No correlation could be established between the blood ketone level and the carbon dioxide combining power of the blood.—*T.H.McG.*

RICHARDSON, R.

The present use of protamine zinc insulin. *Pennsylvania M.J.* 46: 578. 1943.

After 6 years' use of protamine zinc insulin it is increasingly evident that this is the best agent for the control of diabetes. This contribution deals with 100 patients who were transferred from regular insulin to protamine zinc insulin alone or to a combination of both forms of insulin given before breakfast. To secure the fullest use of protamine zinc insulin, the breakfast of each day should be taken care of by the insulin of the previous day. Thus many more patients can be adjusted on a single dose of protamine zinc insulin daily without any quick-acting insulin. When the protamine is given at the beginning of treatment, the author uses from 10 to 20 units, depending on the amount of sugar in the blood and urine. After 3 to 5 days this is increased by 5 to 10 units each 3 days until the result shows in the urine specimens. He then makes the final adjustments by rearranging the meals and, if necessary, by giving an additional small amount of crystalline insulin at the same time as the protamine zinc insulin. Experience with protamine zinc insulin has shown that the advantages following its use are a better adjustment of the patient's diet and insulin and a greater convenience to the patient, as all insulin for the 24 hours is taken at a single time of the day.—*I.B.*

SORKIN, S. Q.

Blood amylase activity in disease of carbohydrate metabolism and in non-diabetic pancreatic disease. *J. Clin. Invest.* 22: 329. 1943.

The author described his own method for determining amyolytic activity, based on the saccharifying power of the enzyme and including fractional splitting as an integral part of the procedure. Normal standards were established in 25 subjects "who had no evidence of organic disease." As compared with these standards, blood amylase values were found to be normal in 56 diabetics, and in 11 patients with hepatocellular liver disease, 8 with other types of liver disturbance, and 1 with glycogen storage disease. Blood amylase values were markedly increased for a brief period of time in 3 patients suffering from acute pancreatic edema. A persistent elevation in the value of blood amylase was observed in 1 patient with a carcinoma of the head of the pancreas. The normal values for blood amylase seen in diseases of carbohydrate metabolism are offered as evidence that that enzyme does not participate in intermediary carbohydrate metabolism.—*T.H.McG.*

SOSKIN, S.

Endocrine disturbances in the regulation of the blood sugar. *Clinics* 1: 1286. 1943.

The maintenance of the blood sugar above certain critical levels is as essential to the living organism as is the continuation of respiration or the persistence of the heart rate. The endocrine glands form an important part of the sugar regulators of the body, which are directed mostly toward the avoidance of hypoglycemia. The author discusses the homeostatic mechanism of the liver, influence of the pancreas, the anterior pituitary, the adrenal cortex and the thyroid, the influence of liver dysfunction on blood sugar regulation, the clinical disturbances in the endocrine regulation of the blood sugar, and the intravenous dextrose tolerance test for liver dysfunction. A useful classification of the endocrine hyperglycemias and hypoglycemias is included.—*I.B.*

PARATHYROID

COPE, O.

Hyperparathyroidism: The significance of general hyperplasia. *Clinics* 1: 1168. 1943.

The case described is the seventh in the author's series, in which the clinical picture was due to hyperplasia rather than tumor of the parathyroids. So rare are the cases due to parathyroid hyperplasia that doctors think of hyperparathyroidism as being always due to "a tumor." If this impression is not dispelled surgeons operating on a case with 4 hyperplastic glands will erroneously excise only 1 gland, with no benefit to the patient. The surgical problem in treating the patient with this pathology is more difficult since it involves doing a subtotal parathyroidectomy.—*I.B.*

ROSE, E.

Hypoparathyroidism. *Clinics* 1: 1179. 1943.

The principal causes of hypoparathyroidism are trauma and accidental removal of the parathyroids incident to thyroidectomy. In many instances acutely developed traumatic tetany is transitory and the symptoms may disappear spontaneously within a few days, weeks, or months, as the remaining parathyroid glands gradually regain their normal function or undergo compensatory hyperfunction. Often the damage is too severe to permit of spontaneous recovery. Untreated, various trophic and metabolic changes are apt to develop. These include lenticular cataract, perivascular cerebral calcification, dryness and brittleness of the hair and nails, dryness of the skin, muscular weakness, constipation, insomnia, psychasthenia, and general slowing of the mental processes. Parathyroid tetany with convulsions may closely simulate epilepsy. Chronic latent hypoparathyroidism may produce a variety of vague misleading symptoms. Numbness and tingling, a feeling of stiffness and slight twitching of the muscles of the face or extremities may be important early signs. Acute hypoparathyroidism may follow the removal of a single hyperfunctioning adenomatous parathyroid gland and should be treated as an emergency. Intravenous injections of calcium gluconate or chloride and proper doses of parathyroid extract are the best therapeutic agents. Most patients eventually become refractory to parathyroid extract. Dihydrotachysterol or large doses of vitamin D are the agents of choice in the treatment of chronic hypoparathyroidism. In excessive dosage, both of these drugs can produce hypercalcemia. Continued maintenance of normal serum calcium levels is essential if the serious trophic and metabolic effects of chronic hypoparathyroidism are to be avoided or arrested.—*I.B.*

SOFFER, L. J., AND C. COHN.

Primary and secondary hyperparathyroidism. *Arch. Int. Med.* 71: 630. 1943.

The authors report 9 cases of hyperparathyroidism. In 5 of these cases the condition was primary, due to adenoma of a parathyroid gland, and in 4 it was secondary, due to chronic renal disease, multiple myeloma and carcinomatous metastasis to the bones. The pathologic physiology, the clinical considerations and the treatment are discussed. The etiology of osteitis fibrosa cystica is usually an adenoma of a parathyroid gland. Occasionally there may be an adenoma of more than 1 parathyroid gland. However, primary hyperparathyroidism may result from hypertrophy of the parathyroids in the absence of actual tumor. The possible existence of a diseased aberrant parathyroid gland located in the mediastinum must be borne in mind.—*I.B.*

WOOD, T. R., AND WM. F. ROSS.

Does the parathyroid hormone influence phosphatase? *J. Am. Chem. Soc.* 64: 2759. 1942.

Parathyroid hormone solution accelerates the liberation of phosphate by kidney phosphatase. This is not attributed to any hormonal activity even in high concentration (75 U per cc. of digest) since other protein solutions or egg serum albumin exhibit the same property.—*D.A.M.*